STN Search

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FILE 'HOME' ENTERED AT 15:23:51 ON 20 JUL 2007

=> fil medline caplus biosis
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                  ENTRY     SESSION
FULL ESTIMATED COST                                0.21        0.21

FILE 'MEDLINE' ENTERED AT 15:24:19 ON 20 JUL 2007

FILE 'CAPLUS' ENTERED AT 15:24:19 ON 20 JUL 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'BIOSIS' ENTERED AT 15:24:19 ON 20 JUL 2007
Copyright (c) 2007 The Thomson Corporation

=> s rhein
L1         1985 RHEIN

=> s diacerein
L2          176 DIACEREIN

=> s diacerhein
L3          113 DIACERHEIN

=> s diacetylrhein
L4          166 DIACETYLRHEIN

=> s Anthraquinones
L5         9950 ANTHRAQUINONES

=> s "il-10"
L6        55751 "IL-10"

=> s (l1 or l2 or l3 orl4) and l6
MISSING OPERATOR L3 ORL4
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s (l1 or l2 or l3 or l4) and l6
L7            1 (L1 OR L2 OR L3 OR L4) AND L6


=> d ibib abs 1-
YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L8   ANSWER 1 OF 4     MEDLINE on STN
ACCESSION NUMBER:    2005415125     MEDLINE Full-text
DOCUMENT NUMBER:     PubMed ID: 15890690
TITLE:               c-Jun N-terminal kinase (JNK) is required for survival and
                     proliferation of B-lymphoma cells.
AUTHOR:              Gururajan Murali; Chui Roger; Karuppannan Anbu K; Ke
                     Jiyuan; Jennings C Darrell; Bondada Subbarao
CORPORATE SOURCE:    Department of Microbiology, Immunology, & Molecular
                     Genetics, University of Kentucky, Lexington, KY, USA.
CONTRACT NUMBER:     AG 05731 (NIA)
```

AI 21490 (NIAID)
CA 92372 (NCI)

SOURCE: Blood, (2005 Aug 15) Vol. 106, No. 4, pp. 1382-91.
Electronic Publication: 2005-05-12.
Journal code: 7603509. ISSN: 0006-4971.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200509

ENTRY DATE: Entered STN: 5 Aug 2005
Last Updated on STN: 20 Sep 2005
Entered Medline: 19 Sep 2005

AB Several primary murine and human B lymphomas and cell lines were found to constitutively express high levels of the activated form of c-jun N-terminal kinase (JNK), a member of the mitogen-activated protein (MAP) kinase family. Proliferation of murine B lymphomas CH31, CH12.Lx, BKS-2, and WEHI-231 and the human B lymphomas BJAB, RAMOS, RAJI, OCI-Ly7, and OCI-Ly10 was strongly inhibited by SP600125, an anthrapyrazolone inhibitor of JNK, in a dose-dependent manner. The lymphoma cells underwent apoptosis and arrested at the G2/M phase of cell cycle. Furthermore, JNK-specific small interfering RNA (siRNA) inhibited the growth of both murine and human B lymphomas. Thus in the B-lymphoma model, JNK appears to have a unique prosurvival role. Survival signals provided by CD40 and interleukin-10 (**IL-10**) together reversed the growth inhibition induced by the JNK inhibitor. c-Myc protein levels were reduced in the presence of both SP600125 and JNK-specific siRNA, and CD40 ligation restored c-Myc levels. Moreover, Bcl-xL rescued WEHI-231 cells from apoptosis induced by the JNK inhibitor. The JNK inhibitor also reduced levels of early growth response gene-1 (Egr-1) protein, and overexpressing Egr-1 partially rescued lymphoma cells from apoptosis. Thus, JNK may act via c-Myc and Egr-1, which were shown to be important for B-lymphoma survival and growth.

L8 ANSWER 2 OF 4 MEDLINE on STN

ACCESSION NUMBER: 2005295894 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 15942676

TITLE: Regulatory effects of emodin on NF-kappaB activation and inflammatory cytokine expression in RAW 264.7 macrophages.

AUTHOR: Li Hai-Long; Chen Hai-Long; Li Hong; Zhang Kai-Li; Chen Xiao-Yan; Wang Xiao-Wei; Kong Qing-You; Liu Jia

CORPORATE SOURCE: Department of Surgery, The First Affiliated Hospital, Dalian Medical University, Dalian, PR China.

SOURCE: International journal of molecular medicine, (2005 Jul) Vol. 16, No. 1, pp. 41-7.
Journal code: 9810955. ISSN: 1107-3756.

PUB. COUNTRY: Greece

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200512

ENTRY DATE: Entered STN: 9 Jun 2005
Last Updated on STN: 20 Dec 2005
Entered Medline: 15 Dec 2005

AB Emodin, an **anthraquinones** component of Rheum palmatun, has been used for anti-inflammatory purposes. However, its underlying molecular effect(s) on target cells remain to be well clarified. Thus, our current study was aimed at

investigating the regulatory mechanism of emodin on liposaccharide-induced inflammatory responses in RAW 264.7 macrophages by RT-PCR, Western blot analysis, immunocytochemical staining and immunofluorescence analysis. It was found that a treatment of 20 microg/ml emodin inhibited the expression of a panel of inflammatory-associated genes, including TNFalpha, iNOS, **IL- 10**, cytosolic IkappaBalpha, IKK-alpha and IKK-gamma, to different extents as well as the nuclear translocation of NF-kappaB (nuclear factor-kappaB). The promoting effect of emodin on the production and translocation of p105 (the precursor of NF-kappaB p50) was time-dependent and reached a maximum at 5 h. Our data suggest that emodin plays its anti-inflammatory roles by regulating inflammatory cytokines, specifically by suppressing NF-kappaB activation.

L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:624566 CAPLUS Full-text
DOCUMENT NUMBER: 143:278778
TITLE: Regulatory effects of emodin on NF-κB activation and inflammatory cytokine expression in RAW 264.7 macrophages
AUTHOR(S): Li, Hai-Long; Chen, Hai-Long; Li, Hong; Zhang, Kai-Li; Chen, Xiao-Yan; Wang, Xiao-Wei; Kong, Qing-You; Liu, Jia
CORPORATE SOURCE: Department of Surgery, The First Affiliated Hospital, Lab of Cell Biology and Molecular Genetics, College of Basic Medical Sciences, Dalian Medical University, Dalian, 116027, Peop. Rep. China
SOURCE: International Journal of Molecular Medicine (2005), 16(1), 41-47
CODEN: IJMMFG; ISSN: 1107-3756
PUBLISHER: International Journal of Molecular Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Emodin, an **anthraquinones** component of Rheum palmatum, has been used for anti-inflammatory purposes. However, its underlying mol. effect(s) on target cells remain to be well clarified. Thus, our current study was aimed at investigating the regulatory mechanism of emodin on liposaccharide-induced inflammatory responses in RAW 264.7 macrophages by RT-PCR, Western blot anal., immunocytochem. staining and immunofluorescence anal. It was found that a treatment of 20 μg/mL emodin inhibited the expression of a panel of inflammatory-associated genes, including TNFα, iNOS, **IL-10**, cytosolic IκBα, IKK-α and IKK-γ, to different extents as well as the nuclear translocation of NF-κB (nuclear factor-κB). The promoting effect of emodin on the production and translocation of p105 (the precursor of NF-κB p50) was time-dependent and reached a maximum at 5 h. Our data suggest that emodin plays its anti-inflammatory roles by regulating inflammatory cytokines, specifically by suppressing NF-κB activation.
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:328366 BIOSIS Full-text
DOCUMENT NUMBER: PREV200510112547
TITLE: Regulatory effects of emodin on NF-kappa B activation and inflammatory cytokine expression in RAW 264.7 macrophages.
AUTHOR(S): Li, Hai-Long [Reprint Author]; Chen, Hai-Long; Li, Hong; Zhang, Kai-Li; Chen, Xiao-Yan; Wang, Xiao-Wei; Kong, Qing-You; Liu, Jia
CORPORATE SOURCE: Dalian Med Univ, Affiliated Hosp 1, Dept Surg, Dalian 116011, Peoples R China

hailong_dl@sina.com
SOURCE: International Journal of Molecular Medicine, (JUL 2005)
Vol. 16, No. 1, pp. 41-47.
ISSN: 1107-3756.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Aug 2005
Last Updated on STN: 25 Aug 2005
AB yEmodin, an **anthraquinones** component of Rheum palmatun, has been used for anti-inflammatory purposes. However, its underlying molecular effect(s) on target cells remain to be well clarified. Thus, our current study was aimed at investigating the regulatory mechanism of emodin on liposaccharide-induced inflammatory responses in RAW 264.7 macrophages by RT-PCR, Western blot analysis, immunocytochemical staining and immunofluorescence analysis. It was found that a treatment of 20 mu g/ml emodin inhibited the expression of a panel of inflammatory-associated genes, including TNF alpha, iNOS, **IL-10**, cystosolic I kappa B alpha, IKK-alpha and IKK-gamma, to different extents as well as the nuclear translocation of NF-kappa B (nuclear factor-kappa B). The promoting effect of emodin on the production and translocation of p105 (the precursor of NF-kappa B p50) was time-dependent and reached a maximum at 5 h. Our data suggest that emodin plays its anti-inflammatory roles by regulating inflammatory cytokines, specifically by suppressing NF-kappa B activation.

```
=> s heme (W) oxidase
L9          63 HEME (W) OXIDASE

=> d hist

     (FILE 'HOME' ENTERED AT 15:23:51 ON 20 JUL 2007)

     FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 15:24:19 ON 20 JUL 2007
L1         1985 S RHEIN
L2          176 S DIACEREIN
L3          113 S DIACERHEIN
L4          166 S DIACETYLRHEIN
L5         9950 S ANTHRAQUINONES
L6        55751 S "IL-10"
L7            1 S (L1 OR L2 OR L3 OR L4) AND L6
L8            4 S L5 AND L6
L9           63 S HEME (W) OXIDASE

=> s "ho-1'
MISMATCHED QUOTE '"HO-1''
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> s "ho-1"
L10        7980 "HO-1"

=> d hist

     (FILE 'HOME' ENTERED AT 15:23:51 ON 20 JUL 2007)

     FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 15:24:19 ON 20 JUL 2007
L1         1985 S RHEIN
L2          176 S DIACEREIN
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L3          113 S DIACERHEIN
L4          166 S DIACETYLRHEIN
L5         9950 S ANTHRAQUINONES
L6        55751 S "IL-10"
L7            1 S (L1 OR L2 OR L3 OR L4) AND L6
L8            4 S L5 AND L6
L9           63 S HEME (W) OXIDASE
L10        7980 S "HO-1"

=> s (l1 or l2 or l3 or l4)
L11       2226 (L1 OR L2 OR L3 OR L4)

=> s l11 and (l9 or l10)
L12          0 L11 AND (L9 OR L10)

=> s (l11 or l5) and (l9 or l10)
L13          4 (L11 OR L5) AND (L9 OR L10)


=> d ibib abs 1-
YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L13  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        1968:476345  CAPLUS Full-text
DOCUMENT NUMBER:         69:76345
TITLE:                   Polarographic and spectral study of derivatives of
                         naphth [2,3-d]imidazole-4,9-dione
AUTHOR(S):               Efros, L. S.; Kul'bitskii, G. N.
CORPORATE SOURCE:        USSR
SOURCE:                  Zhurnal Obshchei Khimii (1968), 38(5), 981-5
                         CODEN: ZOKHA4; ISSN: 0044-460X
DOCUMENT TYPE:           Journal
LANGUAGE:                Russian
GI   For diagram(s), see printed CA Issue.
AB   Anthraquinones with the following substituents: 2-O2N, 1-O2N, 2-Cl, 1-Cl,
     none, 1-HO, 2-H2N, 1-H2N, 1,4-(HO)2, 1,4-H2N(O2N), 1,4-(H2N) HO, 1,4-(H2N)2,
     1,4-(BzNH)2, (p-MeC6H4NH)2-1,4; naphth[2,3-d]imidaxole-4,9-diones (I) with
     substituents: 6-Cl, 5-Cl, 6-HO3S, 5-HO3S, none, and 5-HO; and the 1-methyl
     analogs of these with the following other substituents: 6(7)-O2N, 5(8)-O2N,
     8(5)-O2N, 6(7)-Cl, 5(8)-Cl, 2-Cl, 6(7)-HO3S, 5(8)-HO3S; none, 6(7)-H2N, 2-H2N,
     5(8)-H2N, 8(5)-H2N, 5,8(HO)2, 5,8(H2N)O2N, 5,8-(H2N)HO, 5,8-(H2N)2, 5,8-
     (BzNH)2, and 5,8-(p-MeC6H4NH)2 were examined for ir carbonyl bands and for
     polarographic reduction halfwave potentials.  The tabulated data indicated the
     chemical similarity between these imidazolediones and anthraquinones.


L13  ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        1960:11356  CAPLUS Full-text
DOCUMENT NUMBER:         54:11356
ORIGINAL REFERENCE NO.:  54:2285d-i
TITLE:                   Organic catalysts. LVII. Catalytic action of
                         o-quinones. 6
AUTHOR(S):               Lukowczyk, Bernhard
CORPORATE SOURCE:        Univ. Halle, Germany
SOURCE:                  Journal de Physiologie (Paris, 1946-1992) (1959), 8,
                         372-8
                         CODEN: JOPHAN; ISSN: 0021-7948
DOCUMENT TYPE:           Journal
LANGUAGE:                Unavailable
```

AB cf. C.A. 51, 13828i; 54, 1530g. Polynuclear quinones and bisquinones catalyzed the uptake of O by amino acids. In known ways (Teuber and Gotz, C.A. 49, 13956d) the following anthracenes were converted to the resp. **anthraquinones** (anthracene substituents, quinone substituents, and quinone given): 2,6-HO(KO3S), 7-KO3S, 1,2 (II), orange; 1,8-HO(KO3S) or 1,5-HO(KO3S), 5-KO3S, 1,4 (III), yellow; 1,5-(HO)2 or 1,8(HO)2, 5- **HO**, **1**,4 (IV), yellow-brown, m. 248°; 1,5-(HO)2, 5-**HO**, **1**,2 (V), orange, m. 198°; 2,6-(HO)2, 6- **HO**, **1**,2 (VI), m. 184° (decomposition); 2,7-(HO)2, 7- **HO**, **1**,2 (VII), m. 184° (decomposition). 1,2-Anthraquinone (VIII) brominated 2 days in AcOH yielded 3-bromo-1,2-anthraquinone (IX), carmine-red, m. 238.5° (Me2CO-water). Nitration of VIII in AcOH with 50 volume-% nitric acid yielded 3-nitro-1,2-anthraquinone (X), carmine, m. 182° (AcOH). In the same way as in C.A. 51, 13828i, quinones or quinones and phenols were condensed: from VIII was obtained β-dianthryldiquinhydrone (XI), black with green sheen, m. (20 mm.) 294-6°, transformed to the diquinone in air at 260°; from VI 4-(3,4,7-trihydroxy-1-anthryl)-6- hydroxy-1,2-anthraquinone (XII), color as XI, converted to diquinone at 264°; from VII 4-(3,4,6-trihydroxy-1-anthryl)-7-hydroxy-1,2-anthraquinone (XIII), color as XI, converted to diquinone at 264°; from VIII and 1,2-dihydroxynaphthalene 4-(3,4-dihydroxy-1-naphthyl)-1,2- anthraquinone (XIV), black, converted to diquinone at 280°, m. 380°; from VIII and 2-hydroxyanthracene 4-(2-hydroxy-1-anthryl)-1,2- anthrahydroquinone (XV), color like XI, m. 235-6°, m20 198°; from VIII and 2-phenanthrol 4-(2-hydroxy-1-phenanthryl)-1,2- anthrahydroquinone (XVI), black, m20 292°, converted to orange diquinone at 240-5°, m. 372°; from VIII and 3-phenanthrol 4-(3-hydroxy-4-phenanthryl)-1,2-anthrahydroquinone (XVII), black, m20 312°, converted to orange diquinone at 230-5°, m. 380°; from 3-hydroxy-2-anthroic acid, dl-4-(2-hydroxy-1-anthryl)- 1,2-anthraquinone-2,3'-dicarboxylic acid (uncertain structure) (XVIII), tan, m. above 400°; from 1,2-phenanthrenequinone (XIX), a moss green condensation product, m. 263-5°; from 3,4-phenanthrenequinone an unstable violet powder, m. 240-50°, decompose 270-8°. The cc. of O uptake (in an air atmospheric) of a 10-5 M solution after 4 hrs. alone, with alanine, and with glycine was given: I, 254, 1086, 835; II, 82, 401, 351; III, 332, 329, 350; IV, 320, 344, -; V, 328, 347, -; VI, 247, 465, -; VII, 317, 466, -; IX, 103, 138, 212; X, 110, 165, 305; XI, 46, 700, 881; XII, 294, 819, 909; XIII, 95, 786, 868; XIV, 3, 852, 785; XV, 0, 540, 513; XVI, 56, 640, 928; XVII, 68, 587, 835; XVIII, 53, 124, 322; XIX, 213, 236, -; 1,4-anthraquinone, 241, 281, 322; 1,2-phenanthrenequinone, 199, 192, 218; 3,4-phenanthrenequinone, 120, 118, 216; 3-bromo-1,2- phenanthrenequinone, 164, 183, 189; aceanthracenequinone, 0, 556, -.

L13 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1956:12573 CAPLUS
DOCUMENT NUMBER: 50:12573
ORIGINAL REFERENCE NO.: 50:2677d-g
TITLE: 1-(Hydroxyarylamino)**anthraquinones** and their derivatives
INVENTOR(S): Neresheimer, Heinrich; Krauch, Emil
PATENT ASSIGNEE(S): Badische Anilin- & Soda-Fabrik Akt.-Ges.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 844452		19520721	DE 1942-B6668	19420513

AB Etherified 1-(hydroxyarylamino)**anthraquinones** or their derivs. are treated with acid agents, such as mineral acids or hydrolyzable halides of multivalent metals, at temps. which are insufficient to effect a ceramidonine- or

carbazole-ring closure. The 1-(hydroxyarylamino) **anthraquinones** thus obtained find use as intermediates in the manufacture of dyes. 1-Methylamino-4-(p-methoxyphenylamino)anthraquinone (obtained from 1-methylamino-4-bromoanthraquinone and p-anisidine) 1 part by weight added with stirring to a liquid mixture (I) of 5 parts AlCl3 and 5 parts liquid SO2 which may contain about 10% by weight (based on I) NaCl, and the mixture stirred at room temperature until the MeO radical is completely split off, poured into water, and worked up gives blue 1-methylamino-4-(p- hydroxyphenylamino)anthraquinone of metallic luster. The following **anthraquinones** are similarly prepared (R = p-HOC6H4NH): 4,1-R(**HO**), **1**,8-R2, 1,4,5,6-R2(HO)2, 1,4-R(HO). 4-(p-Hydroxyphenylamino)-N-methyl-1,9-anthrapyridone is obtained from p-EtO analog (prepared from 4-bromo-N-methyl-1,9-anthrapyridone and p-phenetidine).

L13 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1952:52026 CAPLUS
DOCUMENT NUMBER: 46:52026
ORIGINAL REFERENCE NO.: 46:8679e-h
TITLE: Hydroxynitroanthraquinones
INVENTOR(S): Belshaw, Philip L.; Howard, Harold T.; Irving, Francis
PATENT ASSIGNEE(S): Imperial Chemical Industries Ltd.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2587093		19520226	US	

AB An anthraquinone contg. at least 2 halogen or nitro substituents is treated with a metal nitrite in an organic solvent to give a nitrohydroxyanthraquinone. Thus, to 1,5-dichloroanthraquinone 10 and HCONMe2 (I) 100 parts stirred at 140°, was added 10 parts NaNO2 during 1 h., the whole stirred 7-8 h., cooled, poured into 500 cc. H2O, the mixture acidified with HCl, and the resulting suspension stirred at 85-90° and filtered to give 5-nitro-1-hydroxyanthraquinone (II), m. 200° (from I). II in concentrated H2SO4 gave a cherry-red solution Other substituted **anthraquinones** gave related products: 1,5-Cl(O2N), II; 1,5,4,8-Cl2(O2N)2, 4,5,8,1-(O2N)3HO (III), m. 245° (from PhCl); 1,8,4,5-Cl2(O2N)2, III; 1,4,5,8-Cl4, III; 1,4-Cl2, 1,4-O2N(HO) (IV); 1,4-Cl(O2N), IV; 1,4-Br(O2N) (V), IV; 2,3-Cl2, 2,3-O2N(HO) (VI), m. 232-4°; 2,3-Br2, VI; 2,3-Cl(NO2), VI; 1,8-Cl2, 1,8-O2N(HO) (VII), m. 221-3° (from PhCl or I); 1,8-Cl(NO2), VII; 1,5-(O2N)2, II; 1,8,4-Cl2(O2N), 5,4,1-Cl(O2N)HO (VIII), m. 254-6°; and 5,1,4-Cl(O2N)HO (IX), m. 298°; 1,5,4-Cl2(O2N), VIII and IX; 1,2-Cl2, probably 1,2-HO(NO2) (X), m. 193° (from PhCl); 1,2-Cl(O2N), X; 1,3-Cl2, probably 1,3-HO(O2N), m. 238-40° and 1,3-O2N(HO) (isolated as the Me ether); 1,4,8-Cl(O2N)2 or 1,4,5-Cl3, mixture of dinitrohydroxy derivs.; 2,6-Cl2, 2,6-O2N(**HO**); **1** ,5,2-(O2N)2Me, mixture of methylnitrohydroxy derivs.; and dibromoanthanthrone, nitrohydroxyanthanthrone. In place of I may be used aqueous Cellosolve, tetramethylene sulfone, or dimethyltetramethylene sulfone. 1-Bromoanthraquinone 28, 98% H2SO4 250, and 67% HNO3 8 parts, at 10°, gave V.

=> d hist

(FILE 'HOME' ENTERED AT 15:23:51 ON 20 JUL 2007)

FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 15:24:19 ON 20 JUL 2007
L1 1985 S RHEIN

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L2          176 S DIACEREIN
L3          113 S DIACERHEIN
L4          166 S DIACETYLRHEIN
L5         9950 S ANTHRAQUINONES
L6        55751 S "IL-10"
L7            1 S (L1 OR L2 OR L3 OR L4) AND L6
L8            4 S L5 AND L6
L9           63 S HEME (W) OXIDASE
L10        7980 S "HO-1"
L11        2226 S (L1 OR L2 OR L3 OR L4)
L12           0 S L11 AND (L9 OR L10)
L13           4 S (L11 OR L5) AND (L9 OR L10)

=> s modulat?
L14      922259 MODULAT?

=> s l6 and l14
L15        7517 L6 AND L14

=> s l6 (10A) l14
L16        1604 L6 (10A) L14

=> s l6 (5A) l14
L17        1042 L6 (5A) L14

=> s l6 (2A) l14
L18         582 L6 (2A) L14


=> d hist

     (FILE 'HOME' ENTERED AT 15:23:51 ON 20 JUL 2007)

     FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 15:24:19 ON 20 JUL 2007
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L11        2226 S (L1 OR L2 OR L3 OR L4)
L12           0 S L11 AND (L9 OR L10)
L13           4 S (L11 OR L5) AND (L9 OR L10)
L14      922259 S MODULAT?
L15        7517 S L6 AND L14
L16        1604 S L6 (10A) L14
L17        1042 S L6 (5A) L14
L18         582 S L6 (2A) L14

=> s l6.ti.
L19           0 L6.TI.

=> "il-10"/ti
L20        8721 "IL-10"/TI

=> s l6/ti
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L21        8721 L6/TI

=> s l14/ti
L22      280027 L14/TI

=> s l21 (3A) l22
L23         155 L21 (3A) L22



=> s nitric oxide/cn
'CN' IS NOT A VALID FIELD CODE
L25      122941 NITRIC OXIDE/CN

=> s "nitric oxide"
L26      307958 "NITRIC OXIDE"

=> s l26/ti
L27      142829 L26/TI

=> s prostaglandin?
L28      284938 PROSTAGLANDIN?

=> s l28/ti
L29      118466 L28/TI

=> d hist

     (FILE 'HOME' ENTERED AT 15:23:51 ON 20 JUL 2007)

     FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 15:24:19 ON 20 JUL 2007
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L6         55751 S "IL-10"
L7             1 S (L1 OR L2 OR L3 OR L4) AND L6
L8             4 S L5 AND L6
L9            63 S HEME (W) OXIDASE
L10         7980 S "HO-1"
L11         2226 S (L1 OR L2 OR L3 OR L4)
L12            0 S L11 AND (L9 OR L10)
L13            4 S (L11 OR L5) AND (L9 OR L10)
L14       922259 S MODULAT?
L15         7517 S L6 AND L14
L16         1604 S L6 (10A) L14
L17         1042 S L6 (5A) L14
L18          582 S L6 (2A) L14
L19            0 S L6.TI.
L20         8721 "IL-10"/TI
L21         8721 S L6/TI
L22       280027 S L14/TI
L23          155 S L21 (3A) L22
L24          861 S L11/TI
L25       122941 S NITRIC OXIDE/CN
L26       307958 S "NITRIC OXIDE"
L27       142829 S L26/TI
L28       284938 S PROSTAGLANDIN?
L29       118466 S L28/TI
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=> s l24 and l29
L30 22 L24 AND L29

=> duplicate
ENTER REMOVE, IDENTIFY, ONLY, OR (?):remove
ENTER L# LIST OR (END):l30
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS'
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PROCESSING COMPLETED FOR L30
L31 11 DUPLICATE REMOVE L30 (11 DUPLICATES REMOVED)

=> d ibib abs 1-
YOU HAVE REQUESTED DATA FROM 11 ANSWERS - CONTINUE? Y/(N):y

L31 ANSWER 1 OF 11 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:332690 BIOSIS Full-text
DOCUMENT NUMBER: PREV199345027415
TITLE: **Rhein**, an active metabolic product of the natural occurring sennoside laxatives, stimulates chloride secretion by activation of submucosal neurons and release of **prostaglandins** in guinea pig colon.
AUTHOR(S): Frieling, T. [Reprint author]; Rupprecht, C.
CORPORATE SOURCE: Dep. Gastroenterol., Univ. Duesseldorf, Germany
SOURCE: Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A510. Meeting Info.: 94th Annual Meeting of the American Gastroenterological Association. Boston, Massachusetts, USA. May 15-21, 1993.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jul 1993
Last Updated on STN: 31 Aug 1993

L31 ANSWER 2 OF 11 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 93153499 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8094026
TITLE: Influence of **rhein** anthrone on peristaltic reflex of guinea-pig isolated ileum: involvement of **prostaglandins**.
AUTHOR: Nijs G; de Witte P; Geboes K; Meulemans A; Schuurkes J; Lemli J
CORPORATE SOURCE: Laboratory of Pharmaceutical Biology and Phytopharmacology, Institute of Pharmaceutical Sciences, K.U. Leuven, Belgium.
SOURCE: British journal of pharmacology, (1993 Jan) Vol. 108, No. 1, pp. 269-73.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 26 Mar 1993
Last Updated on STN: 6 Feb 1995
Entered Medline: 9 Mar 1993
AB 1 The influence of rhein anthrone on the peristaltic reflex was studied with a modified Trendelenburg technique in a range from 10(-8) M to 4 x 10(-5) M, on

a normal and reversed guinea-pig ileum segment. Rhein anthrone had no significant effects on longitudinal muscle tension, intraluminal pressure or volume displacement when tested on the normal segment in doses up to 10(-5) M. When applied to the mucosal side (reversed segment), rhein anthrone produced a dose-dependent increase of longitudinal muscle tension (significant from 10(-7) M), of intraluminal pressure (significant from 3 x 10(-6) M) and of volume displacement (significant from 10(-7) M). The data show that rhein anthrone possesses in vitro activity which is dependent on contact with the mucosa. 2 The action of rhein anthrone on the reversed segment was inhibited by BW755C (a dual inhibitor of cyclo-oxygenase and lipoxygenase), by indomethacin and by SC19220 (an antagonist of prostaglandin E2 (PGE2) and PGF2 alpha). The effects remaining on longitudinal muscle tension, intraluminal pressure and volume displacement, calculated as percentage (mean +/- s.e.mean) of the initial value, were respectively: 13 +/- 8; 23 +/- 13; 112 +/- 5 for BW755C; 66 +/- 19; 51 +/- 8; 53 +/- 8 for indomethacin and 27 +/- 12; 13 +/- 7; 50 +/- 5 for SC19220. It is concluded that arachidonic acid metabolites, especially PGE2 and PGF2 alpha are involved in the effects of rhein anthrone on the reversed segment.

L31 ANSWER 3 OF 11 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1992:340243 BIOSIS Full-text
DOCUMENT NUMBER: PREV199243029793; BR43:29793
TITLE: THE EFFECTS OF **RHEIN** ANTHRONE ON PERISTALTIC REFLEX OF GUINEA-PIG ILEUM ARE **PROSTAGLANDIN** -MEDIATED.
AUTHOR(S): NIJS G [Reprint author]; DE WITTE P; MEULEMANS A; SCHUURKES J; GEBOES K; LEMLI J
CORPORATE SOURCE: LABORATORY PHARMACEUTICAL BIOLOGY PHYTOPHARMACOLOGY, KU LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1992) Vol. 102, No. 4 PART 2, pp. A230. Meeting Info.: DIGESTIVE DISEASE WEEK AND THE 93RD ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, SAN FRANCISCO, CALIFORNIA, USA, MAY 9-15, 1992. GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 16 Jul 1992
Last Updated on STN: 10 Sep 1992

L31 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 93049693 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1425942
TITLE: Influence of **rhein** anthrone and **rhein** on small intestine transit rate in rats: evidence of **prostaglandin** mediation.
AUTHOR: Nijs G; de Witte P; Geboes K; Lemli J
CORPORATE SOURCE: Laboratory of Pharmaceutical Biology and Phytopharmacology, K.U. Leuven, Belgium.
SOURCE: European journal of pharmacology, (1992 Aug 6) Vol. 218, No. 2-3, pp. 199-203.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 22 Jan 1993

Last Updated on STN: 22 Jan 1993
Entered Medline: 27 Nov 1992

AB The present study was undertaken to investigate the role of prostaglandins in the shortening of transit time observed after intraduodenal administration of rhein anthrone and rhein. After intraduodenal administration of rhein anthrone (0.5-10 mg/rat), a dose-dependent acceleration of small intestinal transit was observed. The effect for rhein (1-10 mg/rat) was far less pronounced. In the same test conditions, analysis of small intestinal tissue revealed a significant increase of prostaglandin E2 (PGE2), reaching its maximum value 30 min after administration of rhein anthrone. The increase in PGE2 found 30 min after administration of rhein was not significant. The effects provoked by rhein anthrone could be largely prevented by pretreatment of the animals with indomethacin (1-3 mg rat) or cortisol (10 mg/rat). It is concluded that prostaglandins play an important role in the acceleration of the transit provoked in rats by rhein anthrone.

L31 ANSWER 5 OF 11 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:380617 BIOSIS Full-text
DOCUMENT NUMBER: PREV199141053007; BR41:53007
TITLE: ROLE OF **PROSTAGLANDIN** E-2 IN THE SECRETION CAUSED BY **RHEIN** ANTHRONE AND **RHEIN** ANTHRAQUINONE IN THE SMALL INTESTINE.
AUTHOR(S): NIJS G [Reprint author]; DE WITTE P; LEMLI J
CORPORATE SOURCE: LAB PHYTOPHARMACOL, INST PHARM SCI, KU LEUVEN, B-3000 LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1991) Vol. 100, No. 5 PART 2, pp. A698.
Meeting Info.: DIGESTIVE DISEASE WEEK AND THE 92ND ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, NEW ORLEANS, LOUISIANA, USA, MAY 19-22, 1991.
GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 17 Aug 1991
Last Updated on STN: 8 Oct 1991

L31 ANSWER 6 OF 11 MEDLINE on STN
ACCESSION NUMBER: 92095038 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1755271
TITLE: Direct and indirect evidence for the involvement of **prostaglandins** in the secretagogue action of **rhein** anthrone in the small intestine.
AUTHOR: Nijs G; de Witte P; Van Hoestenberghe A; Geboes K; Lemli J
CORPORATE SOURCE: Laboratory of Pharmaceutical Biology and Phytopharmacology, Department of Medical Research, K.U. Leuven, Belgium.
SOURCE: Acta gastro-enterologica Belgica, (1991 Mar-Apr) Vol. 54, No. 2, pp. 184-90.
Journal code: 0414075. ISSN: 0001-5644.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199201
ENTRY DATE: Entered STN: 16 Feb 1992
Last Updated on STN: 16 Feb 1992
Entered Medline: 30 Jan 1992

AB The present study was undertaken to investigate the involvement of prostaglandins in the secretagogue action, observed after intraduodenal

administration of rhein anthrone and rhein in rats. After intraduodenal administration of rhein anthrone (50 mg/kg), the active metabolite of sennosides, a very marked increase of secretion was observed compared to control. The amount of secretion was calculated by dividing the total weight of the small intestine, obtained 30 minutes after administration of the drug, by the total length. The effect seen with rhein (50 mg/kg) is far less pronounced than that with rhein anthrone and is not significant when compared with control. Pretreating the animals with indomethacin (15 mg/kg, p.o., 1 hour in advance) or with ibuprofen (15 mg/kg, p.o., 1 hour in advance) largely prevents the secretagogue effect of rhein anthrone, suggesting that prostaglandins play an important role in the observed pharmacological action. This idea is reinforced by the observation that pretreatment with hydrocortisone (50 mg/kg, p.o., 6 hours in advance) is also able to counteract the effect of rhein anthrone. After administration of rhein anthrone, an almost tenfold increase of the tissue content of prostaglandin E2 was observed. Here again, the results with rhein were far less pronounced. It is concluded that prostaglandins play an important role in the secretagogue action of rhein anthrone.

L31 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 1992:144636 CAPLUS Full-text
DOCUMENT NUMBER: 116:144636
TITLE: Characterization of the **prostaglandin** produced due to stimulation by **rhein** anthrone, the active metabolite of sennosides A and B, in mouse colonic tissue
AUTHOR(S): Yagi, Teruyo; Nishikawa, Atsuko; Horiyama, Shizuyo; Miyawaki, Yoshie; Yamauchi, Kazuko; Kuwano, Shigeaki
CORPORATE SOURCE: Fac. Pharm. Sci., Mukogawa Women's Univ., Nishinomiya, 663, Japan
SOURCE: Shoyakugaku Zasshi (1991), 45(2), 163-6
CODEN: SHZAAY; ISSN: 0037-4377
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The amt. of prostaglandin (PG)-like material was increased in the mouse colonic tissue after the intracecal administration of rhein anthrone which is the active metabolite of sennosides A and B. This PGE-like material, which mediated the purgative action, was identified as PGE2 using GC/SIM.

L31 ANSWER 8 OF 11 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 91162462 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1981580
TITLE: **Prostaglandin** E2-mediated stimulation of mucus synthesis and secretion by **rhein** anthrone, the active metabolite of sennosides A and B, in the mouse colon.
AUTHOR: Yagi T; Miyawaki Y; Nishikawa A; Horiyama S; Yamauchi K; Kuwano S
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Hyogo, Japan.
SOURCE: The Journal of pharmacy and pharmacology, (1990 Aug) Vol. 42, No. 8, pp. 542-5.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 5 May 1991
Last Updated on STN: 6 Feb 1995
Entered Medline: 15 Apr 1991

AB Rhein anthrone, the active metabolite of sennosides A and B, stimulated PGE2 release into the mouse colonic lumen. At 6.24 mg kg-1, it decreased net water and Na+ absorption significantly in the case of water, but could not reverse the net absorption in mouse ligated colon, although it enhanced net K+ secretion. Pretreatment with indomethacin diminished the effects of rhein anthrone except on K+ net secretion. Rhein anthrone or PGE2 markedly stimulated mucus secretion and synthesis in mouse ligated colon. The enhanced mucus secretion and synthesis induced by rhein anthrone were significantly suppressed by pretreatment with indomethacin. Our results have shown that the colonic secretion of water and electrolytes mediated by PGE2 is partly involved in the rhein anthrone-induced diarrhoea but that in mice, the mucoid diarrhoea induced by rhein anthrone results mainly from PGE2-mediated mucus synthesis and secretion in the colon.

L31 ANSWER 9 OF 11 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:173993 BIOSIS Full-text
DOCUMENT NUMBER: PREV199140082453; BR40:82453
TITLE: POSSIBLE ROLE OF **PROSTAGLANDINS** IN ACCELERATION OF SMALL INTESTINAL TRANSIT BY **RHEIN** ANTHRONE.
AUTHOR(S): NIJS G [Reprint author]; LEMLI J
CORPORATE SOURCE: LAB FARMACEUTISCHE BIOLOGIE FYTOFARMACOL, KATHOLIEKE UNIV LEUVEN, VAN EVENSTRAAT 4, 3000 LEUVEN, BELGIUM
SOURCE: Planta Medica, (1990) Vol. 56, No. 6, pp. 505-506.
Meeting Info.: MEETING ON BIOLOGY AND CHEMISTRY OF ACTIVE NATURAL SUBSTANCES HELD AT THE INTERNATIONAL JOINT SYMPOSIUM OF THE SOCIETY FOR MEDICINAL PLANT RESEARCH, AMERICAN SOCIETY OF PHARMACOGNOSY, ASSOCIATION FRANCAISE POUR L'ENSEIGNEMENT ET LA RECHERCHE EN PHARMACOGNOSIE (FRENCH ASSOCIATION FOR EDUCATION AND RESEARCH IN PHARMACOGNOSY), AND THE PHYTOCHEMICAL SOCIETY OF EUROPE, BONN, GERMANY, JULY 17-22, 1990. PLANTA MED.
CODEN: PLMEAA. ISSN: 0032-0943.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 16 Apr 1991
Last Updated on STN: 22 May 1991

L31 ANSWER 10 OF 11 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 88214640 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2896769
TITLE: Involvement of **prostaglandin** E-like material in the purgative action of **rhein** anthrone, the intraluminal active metabolite of sennosides A and B in mice.
AUTHOR: Yagi T; Miyawaki Y; Nishikawa T; Yamauchi K; Kuwano S
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Hyogo, Japan.
SOURCE: The Journal of pharmacy and pharmacology, (1988 Jan) Vol. 40, No. 1, pp. 27-30.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 198806
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 14 Jun 1988

AB Intracaecal administration of rhein anthrone, the intraluminally active metabolite of sennosides A and B, to mice quickly induced severe diarrhoea. Pretreatment with the prostaglandin (PG) biosynthesis inhibitor, indomethacin, and PGE2 antagonist, SC-19220, prevented the onset of diarrhoea induced by rhein anthrone, but the PGE2 antagonist polyphoretin phosphate (PPP) showed only a weak inhibitory effect. Rhein anthrone stimulated the production of PGE-like material only in the colon and its large intestinal propulsive activity was depressed by indomethacin and SC-19220, but not by PPP which suggests that the release of PGE-like material has some role in its purgative action.

L31 ANSWER 11 OF 11 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 83215755 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 6133942
TITLE: The influence of **rhein** on the biosynthesis of **prostaglandin**-like substances in-vitro.
AUTHOR: Franchi-Micheli S; Lavacchi L; Friedmann C A; Zilletti L
SOURCE: The Journal of pharmacy and pharmacology, (1983 Apr) Vol. 35, No. 4, pp. 262-4.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198307
ENTRY DATE: Entered STN: 19 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 8 Jul 1983

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YOU HAVE REQUESTED DATA FROM 39 ANSWERS - CONTINUE? Y/(N):y

L36 ANSWER 1 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:696907 CAPLUS Full-text
TITLE: Research on the decreasing function of **rhein** on contractile activity of uterine smooth muscle strips of virginal rats
AUTHOR(S): He, Ye; Ma, Li-yang; Li, Zhi-qiang; Xu, Jing-dong
CORPORATE SOURCE: Department of Physiology, Northwest University for Nationalities, Lanzhou, 730030, Peop. Rep. China
SOURCE: Shenyang Yaoke Daxue Xuebao (2007), 24(4), 242-244, 248
CODEN: SYDXFF; ISSN: 1006-2858
PUBLISHER: Shenyang Yaoke Daxue Xuebao Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB To research the effects of **rhein** on contractile activity of uterine smooth muscle strips of virginal rats. Methods Twenty Wistar virginal rats with the weight of 200 - 250 g were selected. The effects of **rhein** (8.0 + 10-8, 1.6 + 10-7, 3.2 + 10-7, 6.4 + 10-7 g·L-1) on contractile activity of uterine smooth muscle strips of selected virginal rats were recorded. Four antagonists, diphenhydramine (2.0 + 10-6 mol·L-1), phentolamine (2.0 + 10-6 mol·L-1),

verapamil (2.0 + 10-7 mol·L-1), Indomethacin (2.0 + 10-5 mol·L-1) were used to study their mechanisms resp. Results **Rhein** (4.0 + 10-8 g·L-1) could significantly decrease uterine contractile activity of virginal rats and the frequencies, shorten the duration and minish the amplitude of contractile activity. These functions couldn't be blocked by diphenhydramine or phentolamine, but could be blocked by indomethacin and verapamil. Conclusions The effect of **rhein** on contractile activity of uterine smooth muscle strips in rats is probably associated with **prostaglandin** synthese or release, or L-voltage-dependant calcium channels.

L36 ANSWER 2 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:101964 CAPLUS Full-text
DOCUMENT NUMBER: 144:184652
TITLE: Novel pathways in the etiology of cancer, and treatment methods
INVENTOR(S): Benz, Christopher C.
PATENT ASSIGNEE(S): Buck Institute for Age Research, USA
SOURCE: U.S. Pat. Appl. Publ., 49 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006024691	A1	20060202	US 2005-90546		20050324
PRIORITY APPLN. INFO.:			US 2004-556774P	P	20040325
			US 2004-580534P	P	20040616
			US 2004-629691P	P	20041119

AB The invention pertains to the identification of two novel epithelial signaling pathways in ER-pos. breast cancers and the discovery that the cellular biol. and (likely also the clin. outcome) of ER-pos. breast cancer cells is unexpectedly altered when these signaling pathways are activated. The first pathway pertains to the discovery that NF-κB activation and/or DNA binding is implicated in the etiol. of ER-pos. breast (and other) cancers. The second pathway involves ligand-independent quinine-mediated ER activation by phosphorylation (e.g. on SER-118 and SER-167 residues of ER) and nuclear translocation of full-length (67 kDA) ER as well as the phorphorylating activation of a truncated and nuclear-localized ER variant (.apprx.52 kDa). Also disclosed are methods for identifying patients likely to respond to hormonal therapy and for selecting a therapeutic regimen for the treatment of cancer.

L36 ANSWER 3 OF 39 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2006486994 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16912429
TITLE: Inhibition of interleukin-1beta-induced activation of MEK/ERK pathway and DNA binding of NF-kappaB and AP-1: potential mechanism for Diacerein effects in osteoarthritis.
AUTHOR: Domagala F; Martin G; Bogdanowicz P; Ficheux H; Pujol J-P
CORPORATE SOURCE: Laboratoire Negma-Lerads, Toussus-le-Noble, Magny-les-Hameaux Cedex, France.. f.domagala@negma-lerads.fr
SOURCE: Biorheology, (2006) Vol. 43, No. 3-4, pp. 577-87.
Journal code: 0372526. ISSN: 0006-355X.
PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200611
ENTRY DATE: Entered STN: 17 Aug 2006
Last Updated on STN: 10 Nov 2006
Entered Medline: 9 Nov 2006

AB In the present report we have shown that bovine articular chondrocytes cultured in low oxygen tension, i.e. in conditions mimicking their hypoxic in vivo environment, respond to IL-1beta (10 ng/ml) by an increased DNA binding activity of NF-kappaB and AP-1 transcription factors. Incubation of the cells with 10(-5) M **Rhein**, the active metabolite of Diacerhein, for 24 h was found to reduce this activity particularly in the case of AP-1. Mitogen activated kinases (ERK-1 and ERK-2) were activated by exposure of the chondrocytes to a 1 h treatment with IL-1beta. This effect was greater in hypoxia (3% O2) than in normoxia (21% O2). **Rhein** was capable of reducing the IL-1beta-stimulated ERK1/ERK2 pathway whatever the tension of oxygen present in the environment. The mRNA steady-state levels of collagen type II (COL2A1) and aggrecan core protein were found to be significantly increased by a 24-h treatment with 10(-5) M **Rhein**. This stimulating effect was also observed in the presence of IL-1beta, suggesting that the drug could prevent or reduce the IL-1beta-induced inhibition of extra cellular matrix synthesis. IL-1-induced collagenase (MMP1) expression was significantly decreased by **Rhein** under the same conditions. In conclusion, **Rhein** can effectively inhibit the IL-1-activated MAPK pathway and the binding of NF-kappaB and AP-1 transcription factors, two key factors involved in the expression of several pro-inflammatory genes by chondrocytes. In addition, the drug can reduce the procatabolic effect of the cytokine, by reducing the MMP1 synthesis, and enhance the synthesis of matrix components, such as type II collagen and aggrecan. These results may explain the anti-osteoarthritic properties of **Rhein** and its disease-modifying effects on OA cartilage, in spite of the absence of inhibition at **prostaglandin** level.

L36 ANSWER 4 OF 39 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2006037245 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16278282
TITLE: Chondroprotective drugs in degenerative joint diseases.
AUTHOR: Verbruggen G
CORPORATE SOURCE: Polikliniek Reumatologie, 0K12, Universitair Hospitaal, De Pintelaan 185, B-9000 Ghent, Belgium..
gust.verbruggen@ugent.be
SOURCE: Rheumatology (Oxford, England), (2006 Feb) Vol. 45, No. 2, pp. 129-38. Electronic Publication: 2005-11-08. Ref: 145
Journal code: 100883501. ISSN: 1462-0324.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 21 Jan 2006
Last Updated on STN: 7 Mar 2006
Entered Medline: 6 Mar 2006

AB Catabolic cytokine and anabolic growth factor pathways control destruction and repair in osteoarthritis (OA). A unidirectional TNF-alpha/IL-1-driven cytokine cascade disturbs the homeostasis of the extracellular matrix of articular cartilage in OA. Although chondrocytes in OA cartilage overexpress anabolic insulin-like growth factor (IGF) and its specific receptor (IGFRI) autocrine TNF-alpha released by apoptotic articular cartilage cells sets off an auto/paracrine IL-1-driven cascade that overrules the growth factor

activities that sustain repair in degenerative joint disease. Chondroprotection with reappearance of a joint space that had disappeared has been documented unmistakably in peripheral joints of patients suffering from spondyloarthropathy when treated with TNF-alpha-blocking agents that repressed the unidirectional TNF-alpha/IL-1-driven cytokine cascade. A series of connective tissue structure-modifying agents (CTSMAs) that directly affect IL-1 synthesis and release in vitro and down-modulate downstream IL-1 features, e.g. collagenase, proteoglycanase and matrix metalloproteinase activities, the expression of inducible nitric oxide synthase, the increased release of nitric oxide, and the secretion of **prostaglandin** E(2), IL-6 and IL-8, have been shown to possess disease-modifying OA drug (DMOAD) activities in experimental models of OA and in human subjects with finger joint and knee OA. Examples are corticosteroids, some sulphated polysaccharides, chemically modified tetracyclines, diacetylrhein/ **rhein**, glucosamine and avocado/soybean unsaponifiables.

L36 ANSWER 5 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:807117 CAPLUS Full-text
DOCUMENT NUMBER: 145:218004
TITLE: Medicinal composition for lowering endotoxin level in human blood
INVENTOR(S): Han, Dewu; Zhao, Zhengbao; Zhou, Xin; Zhao, Haizhen
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 12pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1695605	A	20051116	CN 2005-10012566	20050602
PRIORITY APPLN. INFO.:			CN 2005-10012566	20050602

AB The title compn. is prepd. from **rhein** 1-25 and danshensu 1-10 weight parts. The composition has the effects in lowering endotoxin level in human blood, blocking biol. effect of endotoxin, and improving liver microcirculation, and can be used for treating intestinal endotoxemia, as well as obstructive jaundice, pancreatitis, and shock accompanied with intestinal endotoxemia.

L36 ANSWER 6 OF 39 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004395691 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15299286
TITLE: Articular chondrocytes cultured in hypoxia: their response to interleukin-1beta and **rhein**, the active metabolite of diacerhein.
AUTHOR: Martin G; Bogdanowicz P; Domagala F; Ficheux H; Pujol J-P
CORPORATE SOURCE: Laboratory of Connective Tissue Biochemistry, Faculty of Medicine, 14032 Caen Cedex, France.
SOURCE: Biorheology, (2004) Vol. 41, No. 3-4, pp. 549-61.
Journal code: 0372526. ISSN: 0006-355X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200412
ENTRY DATE: Entered STN: 10 Aug 2004

Last Updated on STN: 20 Dec 2004
Entered Medline: 14 Dec 2004

AB In the present report, we show that bovine articular chondrocytes cultured in low oxygen tension, i.e. in conditions mimicking their hypoxic in vivo environment, respond to IL-1beta (10 ng/ml) by an increased DNA binding activity of NF-kappaB and AP-1 transcription factors. Incubation of the cells with 10(-5) M **rhein** for 24 h was found to reduce this activity, particularly in the case of AP-1. Mitogen activated kinases (ERK-1 and ERK-2) were activated by exposure of the chondrocytes to 1-h treatment with IL-1beta. This effect was greater in hypoxia (3% O(2)) than in normoxia (21% O(2)). **Rhein** was capable of reducing the IL-1beta-stimulated ERK1/ERK2 pathway whatever the tension of oxygen present in the environment. The mRNA steady-state levels of collagen type II (COL2A1) and aggrecan core protein were found to be significantly increased by a 24-h treatment with 10(-5) M **rhein**. This stimulating effect was also observed in the presence of IL-1beta, suggesting that the drug could prevent or reduce the IL-1beta-induced inhibition of extracellular matrix synthesis. IL-1-induced collagenase (MMP1) expression was significantly decreased by **rhein** in the same conditions. In conclusion, **rhein** can effectively inhibit the IL-1-activated MAPK pathway and the binding of NF-kappaB and AP-1 transcription factors, two key factors involved in the expression of several pro-inflammatory genes by chondrocytes. In addition, the drug can reduce the procatabolic effect of the cytokine, by reducing the MMP1 synthesis, and enhance the synthesis of matrix components, such as type II collagen and aggrecan. These results may explain the anti-osteoarthritic properties of **rhein** and its disease-modifying effects on OA cartilage, in spite of absence of inhibition at **prostaglandin** level.

L36 ANSWER 7 OF 39 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003020282 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12527330
TITLE: Effects of **rhein** on human articular chondrocytes in alginate beads.
AUTHOR: Sanchez Christelle; Mathy-Hartert Marianne; Deberg Michelle A; Ficheux Herve; Reginster Jean Yves L; Henrotin Yves E
CORPORATE SOURCE: Bone and Cartilage Metabolism Research Unit, Institute of Pathology, CHU Sart-Tilman, 4000 Liege, Belgium.
SOURCE: Biochemical pharmacology, (2003 Feb 1) Vol. 65, No. 3, pp. 377-88.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 16 Jan 2003
Last Updated on STN: 14 Feb 2003
Entered Medline: 13 Feb 2003

AB This study was designed to investigate the effects of **rhein**, the active metabolite of diacerhein, on the metabolic functions of human chondrocytes cultured in alginate beads.Enzymatically isolated osteoarthritic (OA) chondrocytes were cultured in alginate beads in a well-defined culture medium for 12 days. **Rhein** was tested in a range of concentrations comprised between 10(-7) and 4 x 10(-5)M, in the presence or absence of 10(-10)M IL-1beta. Interleukin (IL)-6 and -8, macrophage inflammatory protein (MIP-1beta), stromelysin-1 (MMP-3), aggrecan (AGG), tissue inhibitor of metalloproteinases-1 (TIMP-1), **prostaglandin** E(2) (PGE(2)) and nitric oxide (NO) productions were assayed. Cyclooxygenase-2 (COX-2) and inducible NO synthase (iNOS) mRNA steady-state levels were also quantified. In the basal condition, 10(-5)M

rhein increased by 46.5% the production of AGG, decreased by 17-30% the production of IL-6, MMP-3, NO and MIP-1beta but enhanced by 50% the production of PGE(2). IL-1beta increased IL-6, IL-8, MIP-1beta, NO, PGE(2) and MMP-3 productions, but inhibited AGG and TIMP-1 synthesis. **Rhein** partially reversed the effect of IL-1beta on TIMP-1 and NO production, had no effect on AGG, IL-6 and MIP-1beta production, but up-regulated the IL-1beta stimulated PGE(2) production. The COX-2 and iNOS mRNA levels and IL-8 production were not modified by **rhein** .Overall, these results contribute to explain the clinical efficiency of **rhein** and give new information on its mechanisms of action.

L36 ANSWER 8 OF 39 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003465041 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14527176
TITLE: **Rhein** inhibits interleukin-1 beta-induced activation of MEK/ERK pathway and DNA binding of NF-kappa B and AP-1 in chondrocytes cultured in hypoxia: a potential mechanism for its disease-modifying effect in osteoarthritis.
AUTHOR: Martin Gregoire; Bogdanowicz Patrick; Domagala Florence; Ficheux Herve; Pujol Jean-Pierre
CORPORATE SOURCE: Laboratory of Connective Tissue Biochemistry, Faculty of Medicine, Caen Cedex, France.
SOURCE: Inflammation, (2003 Aug) Vol. 27, No. 4, pp. 233-46. Journal code: 7600105. ISSN: 0360-3997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 8 Oct 2003
Last Updated on STN: 27 Apr 2004
Entered Medline: 26 Apr 2004

AB In the present report, we show that bovine articular chondrocytes cultured in low oxygen tension, i.e. in conditions mimicking their hypoxic in vivo environment, respond to IL-1beta (10 ng/mL) by an increased DNA binding activity of NF-kappaB and AP-1 transcription factors. Incubation of the cells with 10(-5) M **rhein** for 24 h was found to reduce this activity, particularly in the case of AP-1. Mitogen activated kinases (ERK-1 and ERK-2) were activated by exposure of the chondrocytes to 1-h treatment with IL-1beta. This effect was greater in hypoxia (3% O2) than in normoxia (21% O2). **Rhein** was capable of reducing the IL-1beta-stimulated ERK1/ERK2 pathway whatever the tension of oxygen present in the environment. The level of c-jun protein, an element of AP-1 complex, was increased by exposure of the chondrocytes to IL-1beta after 2, 6, and 24 h. Addition of **rhein** at 10(-5) M for 24 h did not reduce the c-jun protein amount. The mRNA steady-state levels of collagen type II (COL2A1) and aggrecan core protein were found to be significantly increased by a 24-h treatment with 10(-5) M **rhein**. This stimulating effect was also observed in the presence of IL-1beta, suggesting that the drug could prevent or reduce the IL-1beta-induced inhibition of extracellular matrix synthesis. IL-1-induced collagenase (MMPI) expression was significantly decreased by **rhein** in the same conditions. In conclusion, **rhein** can effectively inhibit the IL-1-activated MAPK pathway and the binding of NF-kappaB and AP-1 transcription factors, two key factors involved in the expression of several proinflammatory genes by chondrocytes. In addition, the drug can reduce the procatabolic effect of the cytokine, by reducing the MMPI synthesis, and enhance the synthesis of matrix components, such as type II collagen and aggrecan. These results may explain the antiosteoarthritic

properties of **rhein** and its disease-modifying effects on OA cartilage, in spite of absence of inhibition at **prostaglandin** level.

L36 ANSWER 9 OF 39 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2002658175 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12391547
TITLE: Inducible nitric oxide synthase inhibitors of Chinese herbs III. Rheum palmatum.
AUTHOR: Wang Ching-Chiung; Huang Yi-Ju; Chen Lih-Geeng; Lee Lain-Tze; Yang Ling-Ling
CORPORATE SOURCE: Graduate Institute of Pharmacognosy Science, Taipei Medical University, Taipei, Taiwan, ROC.
SOURCE: Planta medica, (2002 Oct) Vol. 68, No. 10, pp. 869-74.
Journal code: 0066751. ISSN: 0032-0943.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 7 Nov 2002
Last Updated on STN: 18 Dec 2002
Entered Medline: 17 Dec 2002

AB In this paper, the effects of bioactive compounds of Rheum palmatum L. on the inhibition of NO production from RAW 264.7 cells were explored. Seven main anthraquinone derivatives were isolated from the root of R. palmatum, and of these, emodin and **rhein** significantly inhibited nitrite production from lipopolysaccharide (LPS)-activated RAW 264.7 cells. The IC(50) values for inhibition of nitrite production by emodin and **rhein** were 60.7 and 67.3 microM, respectively. After iNOS enzyme activity was stimulated by LPS for 12 h, treatment with emodin or **rhein** at 20 microg/ml for 18 h did not significantly inhibit NO production. The data show that the inhibitory activity of emodin and **rhein** is not due to direct inhibition of iNOS enzyme activity. However, expression of iNOS and the COX-2 protein was inhibited by emodin in LPS-activated RAW 264.7 cells, and PGE(2) production was reduced. **Rhein** also inhibited LPS-induced iNOS protein expression, but not COX-2 or PGE(2) production. On the other hand, inhibition effects on NO production from RAW 264.7 cells were enhanced and cytotoxic effects decreased by co-treatment with emodin and **rhein**. In conclusion, emodin and **rhein** are major iNOS inhibitors of R. palmatum and may possibly serve as bioactive substances for anti-inflammation effects.

L36 ANSWER 10 OF 39 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2002449539 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12126975
TITLE: Pharmacological studies of diacerein in animal models of inflammation, arthritis and bone resorption.
AUTHOR: Tamura Tadafumi; Shirai Tomomi; Kosaka Nobuo; Ohmori Kenji; Takafumi Nagatomo
CORPORATE SOURCE: Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka-ken 411-8731, Japan.. tadafumi.tamura@kyowa.co.jp
SOURCE: European journal of pharmacology, (2002 Jul 12) Vol. 448, No. 1, pp. 81-7.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 6 Sep 2002
Last Updated on STN: 7 Feb 2003
Entered Medline: 6 Feb 2003

AB Diacerein has proved to be effective in the treatment of osteoarthritis. We investigated the effects of diacerein in animal models of carrageenin-, zymosan-, or dextran-induced paw edema and adjuvant-induced arthritis and in ovariectomized rats. In acute inflammatory models, unlike classical nonsteroidal anti-inflammatory drugs such as naproxen and ibuprofen, diacerein inhibited the rat paw edema induced by various agents. In the adjuvant-induced arthritic rats, diacerein at 100 mg/kg/day significantly suppressed the paw edema and the increase in serum mucoprotein. Addition of 3 mg/kg/day naproxen to each diacerein (3, 10, 30 mg/kg/day) dose resulted in significantly greater anti-inflammatory activity than with naproxen alone. In the ovariectomized rats, diacerein (10, 100 mg/kg/day) also significantly prevented bone loss and reduced the serum alkaline phosphatase and decreased the excretion of urinary hydroxyproline. In addition, **rhein** (10, 30 microM) inhibited calcium release from mouse calvaria induced by interleukin-1 beta, **prostaglandin** E(2) and parathyroid hormone 1-34 human fragment. These findings indicate that diacerein is a novel anti-inflammatory drug with pharmacological properties different from those of classical nonsteroidal anti-inflammatory drugs and support the clinical investigation of the use of combination therapy with diacerein and nonsteroidal anti-inflammatory drugs in patients with not only osteoarthritis but also rheumatoid arthritis.

L36 ANSWER 11 OF 39 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2001447830 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11327257
TITLE: Diacerein reduces the excess synthesis of bone remodeling factors by human osteoblast cells from osteoarthritic subchondral bone.
AUTHOR: Pelletier J P; Lajeunesse D; Reboul P; Mineau F; Fernandes J C; Sabouret P; Martel-Pelletier J
CORPORATE SOURCE: Department of Orhtopedics, H pital St-Luc, Centre Hospitalier de l'Universite de Montreal, H pital Notre-Dame, Quebec, Canada.
SOURCE: The Journal of rheumatology, (2001 Apr) Vol. 28, No. 4, pp. 814-24.
Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 13 Aug 2001
Last Updated on STN: 13 Aug 2001
Entered Medline: 9 Aug 2001

AB OBJECTIVE: Although cartilage degradation characterizes osteoarthritis (OA), there is evidence that remodeling of subchondral bone in this disease is a contributing factor. Therapeutic strategies to modify the metabolism of subchondral bone osteoblasts may be indicated to treat OA. We studied the effects of diacerein and **rhein** on the metabolic and inflammatory variables of OA subchondral osteoblasts. METHODS: Human OA primary subchondral osteoblast cells were used. The effect of diacerein and **rhein** at therapeutic concentrations (5-20 microg/ml) was determined by osteoblast phenotypic factors, alkaline phosphatase, osteocalcin, and cAMP; on metabolic agents

urokinase plasminogen activator (uPA), plasminogen activator inhibitor-1 (PAI-1), and insulin-like growth factor-1 (IGF-1); and on inflammatory mediators interleukin 6 (IL-6), **prostaglandin** E2 (PGE2), and cyclooxygenase-2 (COX-2). RESULTS: Diacerein and **rhein** did not affect either basal and 1,25(OH)2D3 induced alkaline phosphatase or parathyroid hormone (PTH) stimulated cAMP formation. Conversely, they dose dependently and statistically inhibited 1,25(OH)2D3 induced osteocalcin release, a situation explained by a reduction of mRNA levels for osteocalcin. Of the metabolic factors, they inhibited the production of uPA, with **rhein** showing slightly more potency; inhibitions of 69% and 57% were reached at the highest concentration (20 microg/ml) of **rhein** and diacerein, respectively. Both drugs also inhibited the PAI-1 level, albeit at a much lower level than for uPA. Interestingly, determination of the uPA/PAI1 ratio revealed that both drugs inhibited it about 55%, suggesting a decrease in uPA activity. In contrast, IGF-1 levels only increased slightly when cells were treated with **rhein** but not with diacerein. A transient dose dependent effect was found on IL-6 production; an inhibition was noted at low drug concentrations, which returned to basal levels at the highest concentration tested. PGE2 levels increased exponentially and were related to a concomitant increase in COX-2 levels in response to both drugs. CONCLUSION: Our data indicate that diacerein and **rhein** do not appear to affect OA subchondral bone cells' basal cellular metabolism, yet both agents reveal a direct effect at reducing the synthetic activities of osteoblasts, which could be responsible for abnormal subchondral bone remodeling occurring during the course of OA.

L36 ANSWER 12 OF 39 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 2001682996 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11729361
TITLE: Effects of diacerein on indomethacin-induced gastric ulceration.
AUTHOR: Tamura T; Yokoyama T; Ohmori K
CORPORATE SOURCE: Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co., Shizuoka, Japan.. tadafuni.tamura@kyowa.co.jp
SOURCE: Pharmacology, (2001) Vol. 63, No. 4, pp. 228-33.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 3 Dec 2001
Last Updated on STN: 25 Jan 2002
Entered Medline: 8 Jan 2002

AB We investigated the effect of diacerein, an antiosteoarthritic agent, and its metabolite, **rhein**, on the production of reactive oxygen species (ROS) from neutrophils as well as the protective effect of diacerein on indomethacin-induced gastric ulceration and its protection mechanism. **Rhein** inhibited the ROS production from N-formyl-methionyl-leucyl-phenylalanine or phorbol-12-myristate-13-acetate- activated human peripheral neutrophils. Indomethacin-induced gastric ulceration was significantly inhibited by oxygen radical scavengers and 16,16-dimethyl-**prostaglandin** E(2) (dmPGE(2)) but not by allopurinol. Diacerein inhibited indomethacin-induced gastric ulceration in a dose-dependent manner. Diacerein did not affect the gastric mucosal PGE(2) content. In addition, diacerein inhibited HCl + ethanol-induced gastric ulceration. These data indicate that the inhibitory effect of diacerein on indomethacin-induced gastric ulceration could be mediated not by the augmentation of gastric mucosal PGE(2) production but by the suppression of ROS production based on its inhibition of neutrophil activation.

L36 ANSWER 13 OF 39 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 1999074150 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9858439
TITLE: Diacerhein and **rhein** reduce the interleukin 1beta stimulated inducible nitric oxide synthesis level and activity while stimulating cyclooxygenase-2 synthesis in human osteoarthritic chondrocytes.
AUTHOR: Pelletier J P; Mineau F; Fernandes J C; Duval N; Martel-Pelletier J
CORPORATE SOURCE: Rheumatic Disease Unit, Centre hospitalier de l'Universite de Montreal, Quebec, Canada.
SOURCE: The Journal of rheumatology, (1998 Dec) Vol. 25, No. 12, pp. 2417-24.
Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 23 Feb 1999
Last Updated on STN: 23 Feb 1999
Entered Medline: 5 Feb 1999

AB OBJECTIVE: To evaluate the in vitro effects of diacerhein, a new drug for the treatment of osteoarthritis (OA), and its active metabolite, **rhein**, on the production of nitric oxide (NO), **prostaglandin** (PGE2), cyclooxygenase-2 (COX-2), as well as the production and expression of the inducible nitric oxide synthase (iNOS) in human OA chondrocytes. These results were compared to those of the nonsteroidal antiinflammatory drug (NSAID) naproxen. METHODS: Human OA chondrocytes were incubated in the presence or absence of 25 units/ml recombinant human interleukin-1beta (rhIL-1beta) with or without therapeutic concentrations of diacerhein and **rhein** at 5, 10, and 20 microg/ml and naproxen at 30 and 90 microg/ml. Effect of the drugs was also tested on both OA chondrocytes and cartilage explants on increasing IL-1beta concentration (0-100 units/ml). The NO and PGE2 levels were determined in the culture medium using the Griess reaction and a specific ELISA, respectively. Production of COX-2 and synthesis and expression of iNOS were quantitated by Western blot and Northern blot, respectively. RESULTS: The IL- 1beta induced NO production was inhibited by both diacerhein and **rhein** in a time and dose dependent fashion, with statistical significance reached at the therapeutic concentration of 20 microg/ml. A decrease over 80% was found at 24, 48, and 72 h incubation. This was consistent for both chondrocytes and cartilage explants even in the presence of high IL-1beta concentration (100 units/ml). Moreover, this effect appeared to result from iNOS transcriptional and/or post-transcriptional events as indicated by a decrease in this enzyme level for both the mRNA and protein. Naproxen, however, showed only a slight inhibition of IL-1beta induced NO production at the highest dose used, 90 microg/ml. A maximum decrease of 23% in IL-1beta induced NO production was recorded after a 72 h incubation. In contrast to naproxen, which abrogated PGE2 and had no effect on COX-2 synthesis, **rhein** and diacerhein at 5 and 10 microg/ml produced an enhancement in their levels. CONCLUSION: Diacerhein and **rhein**, in contrast to an NSAID, are potent inhibitors of IL-1beta induced NO production by chondrocytes and cartilage, without reducing PGE2 production.

L36 ANSWER 14 OF 39 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 97163896 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9010651

TITLE: Diacerein.
AUTHOR: Spencer C M; Wilde M I
CORPORATE SOURCE: Adis International Limited, Auckland, New Zealand..
demail@adis.co.nz
SOURCE: Drugs, (1997 Jan) Vol. 53, No. 1, pp. 98-106; discussion 107-8. Ref: 45
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 14 Apr 1997
Last Updated on STN: 14 Apr 1997
Entered Medline: 1 Apr 1997

AB **Rhein**, the active metabolite of diacerein, inhibits interleukin-1 activity. Consequently, collagenase production in articular cartilage is reduced. **Rhein** dose-dependently inhibits superoxide anion production, chemotaxis and phagocytic activity of neutrophils, and macrophage migration and phagocytosis. Articular cartilage damage is reduced by diacerein in animal models of osteoarthritis. Diacerein does not alter renal or platelet cyclooxygenase activity and may therefore be tolerated by patients with **prostaglandin**-dependent renal function. In clinical trials of < or = 6 months' duration, oral diacerein 50mg twice daily was associated with improvement in 57 to 85% of patients with osteoarthritis. Pain scores and measures of joint function were generally reduced compared with baseline and placebo. Diacerein had similar efficacy to NSAIDs, but a slower onset of action, in comparative trials of < or = 2 months' duration conducted in patients with osteoarthritis. The predominant adverse effects of diacerein are diarrhoea and related disorders.

L36 ANSWER 15 OF 39 MEDLINE on STN
ACCESSION NUMBER: 95343650 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7618371
TITLE: Laxatives and intestinal epithelial cells: a morphological study of epithelial cell damage and proliferation.
AUTHOR: Geboes K
CORPORATE SOURCE: Departement Medische Beeldvorming en Morfologie, Katholieke Universiteit Leuven.
SOURCE: Verhandelingen - Koninklijke Academie voor Geneeskunde van Belgie, (1995) Vol. 57, No. 1, pp. 51-74; discussion 74-7. Ref: 41
Journal code: 0413210. ISSN: 0302-6469.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 5 Sep 1995
Last Updated on STN: 5 Sep 1995
Entered Medline: 24 Aug 1995

AB Experimental studies indicate that anthranoid laxatives may induce epithelial damage. In addition they induce the release of **prostaglandins**. Epithelial cell damage and release of **prostaglandins** are two pathways by which epithelial cell proliferation could be influenced. Other laxatives including fermentable laxatives like lactulose may also influence large intestine cell proliferation by the trophic effect of the fermentation products such as short chain fatty

acids. For these reasons an in vitro study was performed on human intestinal epithelial cells in culture to investigate the direct damaging effect of **rhein** anthrone. Ultrastructural examination showed a dose dependent direct damage. In addition an in vivo study in rats was performed to compare the short and long term effect of sennosides, bisacodyl, sodium picosulphate and lactulose on epithelial cell proliferation in the ileum and large intestine. Cell proliferation was examined by the BrdUrd labeling technique after 2, 6 and 12 weeks of continuous treatment. Studies in control animals show that the Labeling Index (LI) is higher in the caecum compared with other segments of the colon, and higher in the ileum than in the colon. Treatment with sennosides, bisacodyl and sodium picosulphate does not influence the LI in the ileum and induces no statistically significant increase of the LI when the treated groups are compared with the control group at the end of the study. The proliferative pattern along the crypts remains unchanged with all the laxatives throughout the study. It appears therefore that 'contact' laxatives have no major influence on ileal and colonic epithelial cell proliferation.

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ACCESSION NUMBER: 1994:337632 BIOSIS Full-text
DOCUMENT NUMBER: PREV199497350632
TITLE: The use of **rhein** to augment fluid and electrolyte secretion in the continent jejunal reservoir.
AUTHOR(S): Hade, Debora K.; Kwon, Eugene D.; Stokes, John B.; Williams, Richard D.; Donovan, James F.
CORPORATE SOURCE: Iowa City, IA, USA
SOURCE: Journal of Urology, (1994) Vol. 151, No. 5 SUPPL., pp. 353A.
Meeting Info.: Eighty-ninth Annual Meeting of the American Urological Association. San Francisco, California, USA. May 14-19, 1994.
CODEN: JOURAA. ISSN: 0022-5347.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 1994
Last Updated on STN: 3 Aug 1994

L36 ANSWER 17 OF 39 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1993:332690 BIOSIS Full-text
DOCUMENT NUMBER: PREV199345027415
TITLE: **Rhein**, an active metabolic product of the natural occurring sennoside laxatives, stimulates chloride secretion by activation of submucosal neurons and release of **prostaglandins** in guinea pig colon.
AUTHOR(S): Frieling, T. [Reprint author]; Rupprecht, C.
CORPORATE SOURCE: Dep. Gastroenterol., Univ. Duesseldorf, Germany
SOURCE: Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A510.
Meeting Info.: 94th Annual Meeting of the American Gastroenterological Association. Boston, Massachusetts, USA. May 15-21, 1993.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jul 1993
Last Updated on STN: 31 Aug 1993

L36 ANSWER 18 OF 39 MEDLINE on STN DUPLICATE 12

ACCESSION NUMBER: 93153499 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8094026
TITLE: Influence of **rhein** anthrone on peristaltic reflex of guinea-pig isolated ileum: involvement of **prostaglandins**.
AUTHOR: Nijs G; de Witte P; Geboes K; Meulemans A; Schuurkes J; Lemli J
CORPORATE SOURCE: Laboratory of Pharmaceutical Biology and Phytopharmacology, Institute of Pharmaceutical Sciences, K.U. Leuven, Belgium.
SOURCE: British journal of pharmacology, (1993 Jan) Vol. 108, No. 1, pp. 269-73.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 26 Mar 1993
Last Updated on STN: 6 Feb 1995
Entered Medline: 9 Mar 1993

AB 1 The influence of **rhein** anthrone on the peristaltic reflex was studied with a modified Trendelenburg technique in a range from 10(-8) M to 4 x 10(-5) M, on a normal and reversed guinea-pig ileum segment. **Rhein** anthrone had no significant effects on longitudinal muscle tension, intraluminal pressure or volume displacement when tested on the normal segment in doses up to 10(-5) M. When applied to the mucosal side (reversed segment), **rhein** anthrone produced a dose-dependent increase of longitudinal muscle tension (significant from 10(-7) M), of intraluminal pressure (significant from 3 x 10(-6) M) and of volume displacement (significant from 10(-7) M). The data show that **rhein** anthrone possesses in vitro activity which is dependent on contact with the mucosa. 2 The action of **rhein** anthrone on the reversed segment was inhibited by BW755C (a dual inhibitor of cyclo-oxygenase and lipoxygenase), by indomethacin and by SC19220 (an antagonist of **prostaglandin** E2 (PGE2) and PGF2 alpha). The effects remaining on longitudinal muscle tension, intraluminal pressure and volume displacement, calculated as percentage (mean +/- s.e.mean) of the initial value, were respectively: 13 +/- 8; 23 +/- 13; 112 +/- 5 for BW755C; 66 +/- 19; 51 +/- 8; 53 +/- 8 for indomethacin and 27 +/- 12; 13 +/- 7; 50 +/- 5 for SC19220. It is concluded that arachidonic acid metabolites, especially PGE2 and PGF2 alpha are involved in the effects of **rhein** anthrone on the reversed segment.

L36 ANSWER 19 OF 39 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 94052325 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8234445
TITLE: **Rhein** stimulates electrogenic chloride secretion by activation of submucosal neurons in guinea pig colon.
AUTHOR: Frieling T; Rupprecht C; Schemann M
CORPORATE SOURCE: Department of Gastroenterology, Heinrich Heine University of Dusseldorf, FRG.
SOURCE: Pharmacology, (1993 Oct) Vol. 47 Suppl 1, pp. 70-6.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 17 Jan 1994

Last Updated on STN: 17 Jan 1994
Entered Medline: 20 Dec 1993

AB Conventional flux chamber methods were applied to investigate the mode of action of **rhein**, an active metabolite derived from colonic microbial fermentation of the naturally occurring sennoside laxatives, in muscle-stripped segments of guinea pig colon. Mucosal or serosal application of **rhein** (10 nmol/l to 0.5 mmol/l) resulted in a dose-dependent increase in short-circuit current (Isc) that was superimposed by irregular fluctuations in Isc. The response to electrical field stimulation was increased. The **rhein**-evoked increase in Isc was reduced by serosal addition of 50 mumol/l bumetanide, 1 mumol/l tetrodotoxin, 1 mumol/l atropine and 10 mumol/l piroxicam but not 100 mumol/l hexamethonium, 1 mumol/l ICS 205 930 or 10 mumol/l cimetidine. The study suggests that **rhein** activates chloride secretion by excitation of submucosal neurons and release of acetylcholine and endogenous **prostaglandins**, but not by release of histamine or serotonin.

L36 ANSWER 20 OF 39 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 94052321 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8234441
TITLE: Anthranoids and the mucosal immune system of the colon.
AUTHOR: Geboes K; Spiessens C; Nijs G; de Witte P
CORPORATE SOURCE: Department of Medical Research, KU Leuven, Belgium.
SOURCE: Pharmacology, (1993 Oct) Vol. 47 Suppl 1, pp. 49-57. Ref: 29
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 17 Jan 1994
Entered Medline: 20 Dec 1993

AB The mechanism of action of anthranoids in general and of sennosides at the cellular level is not precisely known. Pseudomelanosis or pseudolipofuscinosis, a condition characterized by the accumulation of pigmented macrophages in the lamina propria, is one of the well-known effects of these products. It is most probably the result of an interaction between apoptotic epithelial cells and the lamina propria cellular infiltrate. Treatment of cell suspensions of intestinal epithelial cells and of human intestinal epithelial cells in culture with **rhein** anthrone, the active compound of sennosides, demonstrates a direct influence of the drug on these epithelial cells. Low doses induce alterations in cellular shape and organelles consistent with increased metabolism. High doses induce apoptotic changes. The interaction between the epithelial cells and cells of the monocyte/macrophage lineages induces also the release of **prostaglandins** of the E series as shown by experiments on cell cultures of epithelial cells and peripheral blood cells. An increase of PGE2 release to about 140% of the control value is noted following administration of low doses of **rhein** anthrone to a combination of human intestinal epithelial cells and human peripheral blood mononuclear cells. This finding indicates that **rhein** anthrone is activating cellular components of the intestinal immune system and may by this pathway induce secretion and motility.

L36 ANSWER 21 OF 39 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 94052320 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7901856

TITLE: In vitro demonstration of a positive effect of **rhein** anthrone on peristaltic reflex of guinea pig ileum.
AUTHOR: Nijs G; de Witte P; Geboes K; Meulemans A; Schuurkes J; Lemli J
CORPORATE SOURCE: Laboratory of Pharmaceutical Biology and Phytopharmacology, KU Leuven, Belgium.
SOURCE: Pharmacology, (1993 Oct) Vol. 47 Suppl 1, pp. 40-8.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 6 Feb 1995
Entered Medline: 20 Dec 1993

AB The influence of **rhein** anthrone on the peristaltic reflex was studied with a modified Trendelenburg technique in the range from 10(-8) to 4 x 10(-5) mol/l, using a normal and reversed guinea pig ileum segment. **Rhein** anthrone had no significant effects on longitudinal muscle tension, intraluminal pressure or volume displacement when tested on the normal segment in doses up to 10(-5) mol/l. When applied to the mucosal side (reversed segment), **rhein** anthrone produced a dose-dependent increase of longitudinal muscle tension, of intraluminal pressure and of volume displacement. The data show that **rhein** anthrone possesses in vitro activity which is dependent on contact with the mucosa. The action of **rhein** anthrone on the reversed segment was inhibited by BW755C (a dual inhibitor of cyclo-oxygenase and lipoxygenase), by indomethacin and by SC19220 (an antagonist of PGE2 and PGF2 alpha). It is concluded that arachidonic acid metabolites, especially PGE2 and PGF2 alpha are involved in the effects of **rhein** anthrone on the reversed segment.

L36 ANSWER 22 OF 39 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 94052312 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8234433
TITLE: Suppression of the purgative action of **rhein** anthrone, the active metabolite of sennosides A and B, by calcium channel blockers, calmodulin antagonists and indomethacin.
AUTHOR: Yamauchi K; Yagi T; Kuwano S
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Nishinomiya, Japan.
SOURCE: Pharmacology, (1993 Oct) Vol. 47 Suppl 1, pp. 22-31.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 17 Jan 1994
Entered Medline: 20 Dec 1993

AB The involvement of Ca2+ in the mechanism of the purgative action of **rhein** anthrone was studied. Among individual or combination pretreatments with calcium channel blockers, calmodulin antagonists and **prostaglandin** biosynthesis inhibitors, the combination of indomethacin and nifedipine completely blocked the diarrhoea induced by **rhein** anthrone and also inhibited

its effects on colonic fluid and electrolyte transport, and large intestinal motility. Calmodulin antagonists were less active regarding suppression of the effects of **rhein** anthrone. We concluded that, in addition to **prostaglandins**, diarrhoea induced by **rhein** anthrone must also involve the calcium channel which can be blocked by nifedipine, but not verapamil.

L36 ANSWER 23 OF 39 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1992:340243 BIOSIS Full-text
DOCUMENT NUMBER: PREV199243029793; BR43:29793
TITLE: THE EFFECTS OF **RHEIN** ANTHRONE ON PERISTALTIC REFLEX OF GUINEA-PIG ILEUM ARE **PROSTAGLANDIN** -MEDIATED.
AUTHOR(S): NIJS G [Reprint author]; DE WITTE P; MEULEMANS A; SCHUURKES J; GEBOES K; LEMLI J
CORPORATE SOURCE: LABORATORY PHARMACEUTICAL BIOLOGY PHYTOPHARMACOLOGY, KU LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1992) Vol. 102, No. 4 PART 2, pp. A230. Meeting Info.: DIGESTIVE DISEASE WEEK AND THE 93RD ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, SAN FRANCISCO, CALIFORNIA, USA, MAY 9-15, 1992. GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 16 Jul 1992
Last Updated on STN: 10 Sep 1992

L36 ANSWER 24 OF 39 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1992:340242 BIOSIS Full-text
DOCUMENT NUMBER: PREV199243029792; BR43:29792
TITLE: ORIGIN OF PGE-2 RELEASE INDUCED BY **RHEIN** ANTHRONE IN INTESTINAL TISSUE AN IN-VITRO STUDY.
AUTHOR(S): NIJS G [Reprint author]; DE WITTE P; GEBOES K; LEMLI J; VANTRAPPEN G
CORPORATE SOURCE: LAB PHARM BIOL PHYTOPHARM, KU LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1992) Vol. 102, No. 4 PART 2, pp. A230. Meeting Info.: DIGESTIVE DISEASE WEEK AND THE 93RD ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, SAN FRANCISCO, CALIFORNIA, USA, MAY 9-15, 1992. GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 16 Jul 1992
Last Updated on STN: 10 Sep 1992

L36 ANSWER 25 OF 39 MEDLINE on STN DUPLICATE 17

ACCESSION NUMBER: 93049693 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1425942
TITLE: Influence of **rhein** anthrone and **rhein** on small intestine transit rate in rats: evidence of **prostaglandin** mediation.
AUTHOR: Nijs G; de Witte P; Geboes K; Lemli J
CORPORATE SOURCE: Laboratory of Pharmaceutical Biology and Phytopharmacology, K.U. Leuven, Belgium.

SOURCE: European journal of pharmacology, (1992 Aug 6) Vol. 218, No. 2-3, pp. 199-203.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 22 Jan 1993
Last Updated on STN: 22 Jan 1993
Entered Medline: 27 Nov 1992

AB The present study was undertaken to investigate the role of **prostaglandins** in the shortening of transit time observed after intraduodenal administration of **rhein** anthrone and **rhein** . After intraduodenal administration of **rhein** anthrone (0.5-10 mg/rat), a dose-dependent acceleration of small intestinal transit was observed. The effect for **rhein** (1-10 mg/rat) was far less pronounced. In the same test conditions, analysis of small intestinal tissue revealed a significant increase of **prostaglandin** E2 (PGE2), reaching its maximum value 30 min after administration of **rhein** anthrone. The increase in PGE2 found 30 min after administration of **rhein** was not significant. The effects provoked by **rhein** anthrone could be largely prevented by pretreatment of the animals with indomethacin (1-3 mg rat) or cortisol (10 mg/rat). It is concluded that **prostaglandins** play an important role in the acceleration of the transit provoked in rats by **rhein** anthrone.

L36 ANSWER 26 OF 39 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:380617 BIOSIS Full-text
DOCUMENT NUMBER: PREV199141053007; BR41:53007
TITLE: ROLE OF **PROSTAGLANDIN** E-2 IN THE SECRETION CAUSED BY **RHEIN** ANTHRONE AND **RHEIN** ANTHRAQUINONE IN THE SMALL INTESTINE.
AUTHOR(S): NIJS G [Reprint author]; DE WITTE P; LEMLI J
CORPORATE SOURCE: LAB PHYTOPHARMACOL, INST PHARM SCI, KU LEUVEN, B-3000 LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1991) Vol. 100, No. 5 PART 2, pp. A698.
Meeting Info.: DIGESTIVE DISEASE WEEK AND THE 92ND ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, NEW ORLEANS, LOUISIANA, USA, MAY 19-22, 1991.
GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 17 Aug 1991
Last Updated on STN: 8 Oct 1991

L36 ANSWER 27 OF 39 MEDLINE on STN
ACCESSION NUMBER: 92108243 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1722344
TITLE: A rapid method for the estimation of **prostaglandin** E2 in intestinal tissues using fluorescence derivatization.
AUTHOR: Nijs G; de Witte P; Lemli J
CORPORATE SOURCE: Laboratory of Pharmaceutical Biology, Katholieke Universiteit Leuven, Belgium.
SOURCE: Prostaglandins, (1991 Nov) Vol. 42, No. 5, pp. 421-9.
Journal code: 0320271. ISSN: 0090-6980.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 2 Mar 1992
Last Updated on STN: 29 Jan 1996
Entered Medline: 7 Feb 1992

AB A sensitive spectrofluorimetric method is described to determine small quantities of **prostaglandin** E2 in complex biological systems as intestinal tissues. The method is based on a solid phase extraction combined with a coupling with a fluorescent marker and measuring the derivatization product by fluorescence densitometry. After mixing the tissue with an ice-cold perchloric acid solution, adjusting the pH, centrifugation and filtration steps, the **prostaglandins** are retained on a solid phase extraction C18 disposable column. They are eluted with diethylether, derivatized with 4-bromomethyl-7-methoxy- coumarin using potassium carbonate as condensating agent and finally analysed using fluorescence densitometry on silica gel TLC plates. Applying this method, amounts down to 5 ng (per gram wet tissue) could be measured in intestinal tissues, the s.e.m. for replicated total analysis being less than 15%. The foregoing method is applied for the determination of PGE2 released in the intestinal wall under the influence of laxatives.

L36 ANSWER 28 OF 39 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 91374265 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1680171
TITLE: Suppression of the purgative action of **rhein** anthrone, the active metabolite of sennosides A and B, by indomethacin in rats.
AUTHOR: Yagi T; Miyawaki Y; Nishikawa A; Yamauchi K; Kuwano S
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Hyogo, Japan.
SOURCE: The Journal of pharmacy and pharmacology, (1991 May) Vol. 43, No. 5, pp. 307-10.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 8 Nov 1991
Last Updated on STN: 6 Feb 1995
Entered Medline: 24 Oct 1991

AB **Rhein** anthrone (12.48 mg kg-1) produces watery and mucoid diarrhoea approximately 20 min after intracaecal administration to rats. Pretreatment with the **prostaglandin** (PG) biosynthesis inhibitor indomethacin (10 mg kg-1, i.p.) only delayed and did not completely block the onset of the induced diarrhoea. **Rhein** anthrone stimulated PGE2 release into the rat colonic lumen and the increased release was depressed by indomethacin. **Rhein** anthrone also accelerated large intestinal transit and this acceleration could be partly inhibited by indomethacin, which was probably responsible for the delay in the onset of diarrhoea. Indomethacin prevented the enhanced water, K+ and mucus secretion and the reduced Na+ absorption in the colon which were induced by **rhein** anthrone. The net water secretion could not be reversed to net absorption and the mucus secretion was only slightly depressed by indomethacin. Thus, our findings suggest that other mechanisms, together with the PG-dependent mechanism, are involved in the purgative action of **rhein** anthrone in rats.

L36 ANSWER 29 OF 39 MEDLINE on STN

ACCESSION NUMBER: 92095038 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1755271
TITLE: Direct and indirect evidence for the involvement of **prostaglandins** in the secretagogue action of **rhein** anthrone in the small intestine.
AUTHOR: Nijs G; de Witte P; Van Hoestenberghe A; Geboes K; Lemli J
CORPORATE SOURCE: Laboratory of Pharmaceutical Biology and Phytopharmacology, Department of Medical Research, K.U. Leuven, Belgium.
SOURCE: Acta gastro-enterologica Belgica, (1991 Mar-Apr) Vol. 54, No. 2, pp. 184-90.
Journal code: 0414075. ISSN: 0001-5644.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199201
ENTRY DATE: Entered STN: 16 Feb 1992
Last Updated on STN: 16 Feb 1992
Entered Medline: 30 Jan 1992

AB The present study was undertaken to investigate the involvement of **prostaglandins** in the secretagogue action, observed after intraduodenal administration of **rhein** anthrone and **rhein** in rats. After intraduodenal administration of **rhein** anthrone (50 mg/kg), the active metabolite of sennosides, a very marked increase of secretion was observed compared to control. The amount of secretion was calculated by dividing the total weight of the small intestine, obtained 30 minutes after administration of the drug, by the total length. The effect seen with **rhein** (50 mg/kg) is far less pronounced than that with **rhein** anthrone and is not significant when compared with control. Pretreating the animals with indomethacin (15 mg/kg, p.o., 1 hour in advance) or with ibuprofen (15 mg/kg, p.o., 1 hour in advance) largely prevents the secretagogue effect of **rhein** anthrone, suggesting that **prostaglandins** play an important role in the observed pharmacological action. This idea is reinforced by the observation that pretreatment with hydrocortisone (50 mg/kg, p.o., 6 hours in advance) is also able to counteract the effect of **rhein** anthrone. After administration of **rhein** anthrone, an almost tenfold increase of the tissue content of **prostaglandin** E2 was observed. Here again, the results with **rhein** were far less pronounced. It is concluded that **prostaglandins** play an important role in the secretagogue action of **rhein** anthrone.

L36 ANSWER 30 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 19
ACCESSION NUMBER: 1992:144636 CAPLUS Full-text
DOCUMENT NUMBER: 116:144636
TITLE: Characterization of the **prostaglandin** produced due to stimulation by **rhein** anthrone, the active metabolite of sennosides A and B, in mouse colonic tissue
AUTHOR(S): Yagi, Teruyo; Nishikawa, Atsuko; Horiyama, Shizuyo; Miyawaki, Yoshie; Yamauchi, Kazuko; Kuwano, Shigeaki
CORPORATE SOURCE: Fac. Pharm. Sci., Mukogawa Women's Univ., Nishinomiya, 663, Japan
SOURCE: Shoyakugaku Zasshi (1991), 45(2), 163-6
CODEN: SHZAAY; ISSN: 0037-4377
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The amt. of **prostaglandin** (PG)-like material was increased in the mouse colonic tissue after the intracecal administration of **rhein** anthrone which is the active metabolite of sennosides A and B. This PGE-like material, which mediated the purgative action, was identified as PGE2 using GC/SIM.

L36 ANSWER 31 OF 39 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 91162462 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1981580
TITLE: **Prostaglandin** E2-mediated stimulation of mucus synthesis and secretion by **rhein** anthrone, the active metabolite of sennosides A and B, in the mouse colon.
AUTHOR: Yagi T; Miyawaki Y; Nishikawa A; Horiyama S; Yamauchi K; Kuwano S
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Hyogo, Japan.
SOURCE: The Journal of pharmacy and pharmacology, (1990 Aug) Vol. 42, No. 8, pp. 542-5.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 5 May 1991
Last Updated on STN: 6 Feb 1995
Entered Medline: 15 Apr 1991

AB **Rhein** anthrone, the active metabolite of sennosides A and B, stimulated PGE2 release into the mouse colonic lumen. At 6.24 mg kg-1, it decreased net water and Na+ absorption significantly in the case of water, but could not reverse the net absorption in mouse ligated colon, although it enhanced net K+ secretion. Pretreatment with indomethacin diminished the effects of **rhein** anthrone except on K+ net secretion. **Rhein** anthrone or PGE2 markedly stimulated mucus secretion and synthesis in mouse ligated colon. The enhanced mucus secretion and synthesis induced by **rhein** anthrone were significantly suppressed by pretreatment with indomethacin. Our results have shown that the colonic secretion of water and electrolytes mediated by PGE2 is partly involved in the **rhein** anthrone-induced diarrhoea but that in mice, the mucoid diarrhoea induced by **rhein** anthrone results mainly from PGE2-mediated mucus synthesis and secretion in the colon.

L36 ANSWER 32 OF 39 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:173993 BIOSIS Full-text
DOCUMENT NUMBER: PREV199140082453; BR40:82453
TITLE: POSSIBLE ROLE OF **PROSTAGLANDINS** IN ACCELERATION OF SMALL INTESTINAL TRANSIT BY **RHEIN** ANTHRONE.
AUTHOR(S): NIJS G [Reprint author]; LEMLI J
CORPORATE SOURCE: LAB FARMACEUTISCHE BIOLOGIE FYTOFARMACOL, KATHOLIEKE UNIV LEUVEN, VAN EVENSTRAAT 4, 3000 LEUVEN, BELGIUM
SOURCE: Planta Medica, (1990) Vol. 56, No. 6, pp. 505-506.
Meeting Info.: MEETING ON BIOLOGY AND CHEMISTRY OF ACTIVE NATURAL SUBSTANCES HELD AT THE INTERNATIONAL JOINT SYMPOSIUM OF THE SOCIETY FOR MEDICINAL PLANT RESEARCH, AMERICAN SOCIETY OF PHARMACOGNOSY, ASSOCIATION FRANCAISE POUR L'ENSEIGNEMENT ET LA RECHERCHE EN PHARMACOGNOSIE (FRENCH ASSOCIATION FOR EDUCATION AND RESEARCH IN PHARMACOGNOSY), AND THE PHYTOCHEMICAL SOCIETY OF EUROPE, BONN, GERMANY, JULY 17-22, 1990. PLANTA MED.
CODEN: PLMEAA. ISSN: 0032-0943.
DOCUMENT TYPE: Conference; (Meeting)

FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 16 Apr 1991
Last Updated on STN: 22 May 1991

L36 ANSWER 33 OF 39 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 90076358 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2512175
TITLE: Effects of **rhein** on renal arachidonic acid metabolism and renal function in patients with congestive heart failure.
AUTHOR: La Villa G; Marra F; Laffi G; Belli B; Meacci E; Fascetti P; Gentilini P
CORPORATE SOURCE: Istituto di Clinica Medica II, University of Florence School of Medicine, Pisa, Italy.
SOURCE: European journal of clinical pharmacology, (1989) Vol. 37, No. 1, pp. 1-5.
Journal code: 1256165. ISSN: 0031-6970.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199001
ENTRY DATE: Entered STN: 28 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 23 Jan 1990

AB In a randomized double-blind cross-over study the effects of **rhein** (administered as diacetyl-**rhein** 50 mg b.d. for 5 days) and placebo on renal arachidonic acid metabolism and renal function have been compared in 12 elderly patients (mean age 75.2 years) with congestive heart failure, whose renal function was known to be dependent on the integrity of the renal **prostaglandin** system. **Rhein** like placebo, did not induce any change in the urinary excretion of **prostaglandin** (PG) E2, 6-keto-PGF1 alpha and thromboxane (TX) B2, nor did it affect creatinine clearance, blood urea, urine output, natriuresis, body weight, plasma renin activity or plasma aldosterone concentration. Separate analysis of the results obtained in the 5 patients receiving diuretic treatment did not show any significant effect of **rhein** as compared with placebo on the parameters investigated. Serum TXB2 concentration during whole blood clotting, as an index of platelet arachidonic acid metabolism, also showed no significant difference when DAR and placebo were compared. It is concluded that in patients with congestive heart failure **rhein** does not inhibit renal or platelet eicosanoid metabolism, nor does it modify renal function, sodium excretion or the renal response to diuretics.

L36 ANSWER 34 OF 39 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 88218043 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3368508
TITLE: Effect of **rhein** on electrogenic chloride secretion in rabbit distal colon.
AUTHOR: Clauss W; Domokos G; Leng-Peschlow E
CORPORATE SOURCE: Institut fur Veterinarphysiologie, Freie Universitat Berlin, BRD.
SOURCE: Pharmacology, (1988) Vol. 36 Suppl 1, pp. 104-10.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198806
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 8 Mar 1990
Entered Medline: 22 Jun 1988

AB The effect of the laxative component **rhein** on electrical properties and Cl transport was investigated in partially stripped epithelial sheets of rabbit distal colon under short-circuit conditions. Whereas mucosal **rhein** had no effect, serosally applied **rhein** stimulated electrogenic Cl secretion in a dose-dependent manner with a half-maximal stimulation at 0.05 mmol/l. The stimulation was partially reversible by serosal bumetanide. Indomethacin preincubation inhibited the effect of **rhein**, but did not prevent theophylline-induced Cl secretion. The results suggest a **prostaglandin**-mediated effect of **rhein** on the apical Cl conductance of the colonic cells.

L36 ANSWER 35 OF 39 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 88214640 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2896769
TITLE: Involvement of **prostaglandin** E-like material in the purgative action of **rhein** anthrone, the intraluminal active metabolite of sennosides A and B in mice.
AUTHOR: Yagi T; Miyawaki Y; Nishikawa T; Yamauchi K; Kuwano S
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Hyogo, Japan.
SOURCE: The Journal of pharmacy and pharmacology, (1988 Jan) Vol. 40, No. 1, pp. 27-30.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198806
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 14 Jun 1988

AB Intracaecal administration of **rhein** anthrone, the intraluminally active metabolite of sennosides A and B, to mice quickly induced severe diarrhoea. Pretreatment with the **prostaglandin** (PG) biosynthesis inhibitor, indomethacin, and PGE2 antagonist, SC-19220, prevented the onset of diarrhoea induced by **rhein** anthrone, but the PGE2 antagonist polyphoretin phosphate (PPP) showed only a weak inhibitory effect. **Rhein** anthrone stimulated the production of PGE-like material only in the colon and its large intestinal propulsive activity was depressed by indomethacin and SC-19220, but not by PPP which suggests that the release of PGE-like material has some role in its purgative action.

L36 ANSWER 36 OF 39 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 88197541 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3448025
TITLE: Studies in vitro on the effects of **rhein** on the chemotaxis of human leukocytes.
AUTHOR: Mian M; Azzara' A; Benetti D; Ruocco L; Bertelli A; Ambrogi F
CORPORATE SOURCE: Institute of Pharmacology, University of Pisa, Italy.
SOURCE: International journal of tissue reactions, (1987) Vol. 9, No. 6, pp. 459-63.

Journal code: 8302116. ISSN: 0250-0868.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198805
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 8 Mar 1990
Entered Medline: 31 May 1988

AB **Rhein** (R: 1,8-dihydroxy-3-carboxyanthraquinone) is the active metabolite of the drug diacetylrhein (DAR), an anthraquinone molecule which has recently been proposed for the long-term treatment of osteoarthrosis. Its action mechanism in rheumatic pathology has not been fully explained. It is known that DAR, while not inhibiting the formation of **prostaglandins**, inhibits certain proteolytic enzymes, and acts on phlogistic cells by lysosomal enzymic and superoxide-anion modifications. Moreover DAR modifies phagocytic functions and the motility of cells. This paper is a contribution to the clarification of the last point, namely the effect of **rhein** on cell motility. It reports that in vitro no effect of R on random migration was found, but instead a double inhibiting effect on chemotaxis (i.e. a low-dosage and a high-dosage effect). Furthermore, R did not modify the inhibition or induce modification of chemotaxis by vinblastine. Finally R cancelled the stimulating effect of ionic potassium. The results thus indicate that R acts on the chemotaxis of the leukocytes with a complex action at different doses. The action mechanism is probably due to a membrane effect, since **rhein** (R) did not modify the chemotaxis-inhibiting activity of vinblastine but did interfere with the stimulating effect of K+.

L36 ANSWER 37 OF 39 MEDLINE on STN DUPLICATE 25
ACCESSION NUMBER: 86226998 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2872313
TITLE: Acceleration of large intestine transit time in rats by sennosides and related compounds.
AUTHOR: Leng-Peschlow E
SOURCE: The Journal of pharmacy and pharmacology, (1986 May) Vol. 38, No. 5, pp. 369-73.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198607
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 23 Jul 1986

AB Sennosides A + B and their natural metabolites, sennidins A + B, rheinanthrone and **rhein**, as well as the synthetic laxative danthron, were investigated for their influence on small and large intestine transit time in rats. Carmine red, as a marker, was administered through a gastric tube for small intestine transit or intracaecally by a chronically implanted catheter for colon transit. High doses of sennosides (250-500 mg kg-1) given orally from 20 min or up to 6 h before marker administration had no effect on small intestine transit time. The metabolites and danthron (10-100 mg kg-1 p.o.) also did not accelerate upper gastrointestinal passage. Intracaecal administration at the same time as carmine red, however, reduced the time for the appearance of the first coloured faeces from more than 8 h in the controls to 46 +/- 9 min after sennosides, 34 +/- 11 min after sennidins, 53 +/- 83 min after **rhein** and 16 +/- 4 min after rheinanthrone (50 mg kg-1 of each). Danthron was ineffective. Thus, sennosides and their natural metabolites specifically influence large

intestinal motility. Acceleration of colonic transport seems to be a major component of the laxative action whereas for danthron motility changes are not responsible for its laxative action. Indomethacin partly inhibited the acceleration of large intestine transit induced by sennosides. An involvement of endogenous **prostaglandins** may therefore be possible, although a local bolus administration of PGF2 alpha or PGE2 into the caecal lumen neither influenced transit time nor induced diarrhoea.

L36 ANSWER 38 OF 39 MEDLINE on STN DUPLICATE 26
ACCESSION NUMBER: 83215755 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 6133942
TITLE: The influence of **rhein** on the biosynthesis of **prostaglandin**-like substances in-vitro.
AUTHOR: Franchi-Micheli S; Lavacchi L; Friedmann C A; Zilletti L
SOURCE: The Journal of pharmacy and pharmacology, (1983 Apr) Vol. 35, No. 4, pp. 262-4.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198307
ENTRY DATE: Entered STN: 19 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 8 Jul 1983

L36 ANSWER 39 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 27
ACCESSION NUMBER: 1976:159826 CAPLUS Full-text
DOCUMENT NUMBER: 84:159826
TITLE: On the molecular structure of receptors for co-carcinogens and some anti-cancer drugs
AUTHOR(S): Smythies, J. R.; Benington, F.; Morin, R. D.
CORPORATE SOURCE: Dep. Psychiatry, Univ. Alabama, Birmingham, AL, USA
SOURCE: Psychoneuroendocrinology (1975), 1(2), 123-30
CODEN: PSYCDE; ISSN: 0306-4530
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A **prostaglandin** receptor model is presented using the basic Kusnetsov-Ghokov model based on 2 parallel protein β-chains. A comparison of compds. with biol. activity suggests that the violent cathartic such as **rhein** and ricinoleic acid and the cocarcinogens such as thorbol myristate acetate should fit the receptor and the **prostaglandin** agonists, whereas antitumor agents such as maytansine and acromycine should be **prostaglandin** antagonists.

=> d l39 ibib abs 1-10

L39 ANSWER 1 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:583743 CAPLUS Full-text
TITLE: Differential Responses of the Nrf2-Keap1 System to Laminar and Oscillatory Shear Stresses in Endothelial Cells. [Erratum to document cited in CA143:112886]
AUTHOR(S): Hosoya, Tomonori; Maruyama, Atsushi; Kang, Moon-Il; Kawatani, Yukie; Shibata, Takahiro; Uchida, Koji; Itoh, Ken; Yamamoto, Masayuki
CORPORATE SOURCE: Environmental Response Project ERATO-Japan Science and

Technology Agency, Graduate School of Comprehensive Human Sciences and Center for Tsukuba Advanced Research Alliance, University of Tsukuba, Tsukuba, 305-8575, Japan
SOURCE: Journal of Biological Chemistry (2007), 282(20), 15312
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal; Errata
LANGUAGE: English
AB On page 27245, under the "Exptl. Procedures" heading and the "Transfection of siRNA" sub-heading, the first sentence should read: "Nrf2 siRNA (50 and 100 nM) was transfected into Haec by Oligofectamine (Invitrogen) 24 h prior to flow exposure.".

=> d l39 ibib abs 131

L39 ANSWER 131 OF 131 MEDLINE on STN DUPLICATE 65
ACCESSION NUMBER: 96000222 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7556684
TITLE: Involvement of protein kinase in delta 12-**prostaglandin** J2-induced expression of rat heme oxygenase-1 gene.
AUTHOR: Negishi M; Odani N; Koizumi T; Takahashi S; Ichikawa A
CORPORATE SOURCE: Department of Physiological Chemistry, Faculty of Pharmaceutical Sciences, Kyoto University, Japan.
SOURCE: FEBS letters, (1995 Sep 25) Vol. 372, No. 2-3, pp. 279-82.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 27 Dec 1995
Last Updated on STN: 6 Feb 1998
Entered Medline: 13 Nov 1995
AB We recently identified the cis-regulatory element and its specific nuclear binding factors for delta 12-**prostaglandin** (PG) J2-induced expression of the rat heme oxygenase, **HO-1** [Koizumi, T., Odani, N., Okuyama, T., Ichikawa, A. and Negishi, M. (1995) J. Biol. Chemical 270, in press]. Here we further examined the molecular mechanism underlying the delta 12-PGJ2-induced **HO-1** gene expression. Protein kinase inhibitors, 2-aminopurine and staurosporine, suppressed the delta 12-PGJ2-induced **HO-1** mRNA and the nuclear protein binding to the delta 12-PGJ2-responsive cis-regulatory element in rat basophilic leukemia cells. Furthermore, the nuclear protein binding to the element was suppressed by in vitro phosphatase treatment of the nuclear proteins from delta 12-PGJ2-treated cells. These findings suggest that delta 12-PGJ2 induces the expression of the **HO-1** gene through phosphorylation of the nuclear proteins which bind to the delta 12-PGJ2-responsive element.

=> d l39 ibib abs 100

L39 ANSWER 100 OF 131 MEDLINE on STN DUPLICATE 52
ACCESSION NUMBER: 2002266513 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12006176
TITLE: Activation of the mouse heme oxygenase-1 gene by 15-deoxy-Delta(12,14)-**prostaglandin** J(2) is mediated by the stress response elements and transcription factor Nrf2.
AUTHOR: Gong Pengfei; Stewart Daniel; Hu Bin; Li Ning; Cook Julia; Nel Andre; Alam Jawed
CORPORATE SOURCE: Department of Molecular Genetics, Alton Ochsner Medical Foundation, New Orleans, LA 70121, USA.
CONTRACT NUMBER: AI-50495 (NIAID)
DK-43135 (NIDDK)
ES-10553 (NIEHS)
SOURCE: Antioxidants & redox signaling, (2002 Apr) Vol. 4, No. 2, pp. 249-57.
Journal code: 100888899. ISSN: 1523-0864.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 14 May 2002
Last Updated on STN: 14 Sep 2002
Entered Medline: 13 Sep 2002

AB The mechanism of heme oxygenase-1 (**ho-1**) gene activation by 15-deoxy-Delta(12,14)-**prostaglandin** J(2) (15d-PGJ(2)) was examined. 15d-PGJ(2) stimulated expression of **HO -1** mRNA and protein and of a mouse **ho-1** gene promoter/luciferase fusion construct (HO15luc) in a dose-dependent manner in mouse hepatoma (Hepa) cells. HO15luc expression was not effected by troglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR-gamma) ligand, but induction by 15d-PGJ(2) was abrogated by the antioxidant N-acetylcysteine. The primary 15d-PGJ(2) responsive sequences were localized to a 5' distal enhancer (E1) and identified as the stress-response element, previously shown to mediate **ho- 1** activation by several agents, including heme and heavy metals. Treatment of Hepa cells with 15d-PGJ(2) stimulated stress-response element-binding activity as judged by electrophoretic mobility shift assays. Antibody "supershift" experiments identified NF-E2 related factor 2 (Nrf2), but not Fos, Jun, or activating transcription factor/cyclic AMP response element binding protein transcription factors, within the 15d-PGJ(2)-induced complexes. Similarly, a dominant-negative mutant of Nrf2, but not of c-Jun or c-Fos, abrogated 15d-PGJ(2)-stimulated E1 transcription activity. Finally, prior induction of **HO- 1** in RAW264.7 mouse macrophages by 15d-PGJ(2) attenuated cell death caused by diesel exhaust particle extracts. These results demonstrate that induction of mouse **HO-1** expression by 15d-PGJ(2) is independent of PPAR-gamma but dependent on oxidative stress, is regulated by the oxidative stress-activated transcription factor Nrf2, and provides cytoprotective activity.

=> d 139 ibib abs 90

L39 ANSWER 90 OF 131 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:19431 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400011306
TITLE: COX-2 Inhibition Prevents Heme Oxygenase-1 Expression in Human Microvascular Endothelial Cells.
AUTHOR(S): Armstead, Valerie E. [Reprint Author]; Powell, Garry

[Reprint Author]
CORPORATE SOURCE: Anesthesiology, Thomas Jefferson University/Jefferson Med. College, Philadlephia, PA, USA
SOURCE: Anesthesiology Abstracts of Scientific Papers Annual Meeting, (2003) No. 2003, pp. Abstract No. A-669. http://www.asa-abstracts.com. cd-rom.
Meeting Info.: 2003 Annual Meeting of the American Society of Anesthesiologists. San Francisco, CA, USA. October 11-15, 2003. American Society of Anesthesiologists.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003

AB Introduction:Heme oxygenase-1 (**HO-1**) is a key enzyme in heme catabolism, oxidatively clearing heme to yield biliverdin, iron, and carbon monoxide. Inhibition of heme oxygenase causes an elevation of blood pressure in rats, suggesting that carbon monoxide serves a vasodepressive function. In the present study, we investigated **HO -1** expression in human microvascular endothelial cells in the presence and absence of COX-2 inhibition (Coxibs). Methods: Human adipose microvascular endothelial cells (HADMEC) were cultured and grown to confluence. To elicit a measurable **HO-1** response the HADMEC were stimulated with lipopolysaccharide (LPS) (10 ng/mL). A separate group of cells were pre-treated with the COX-2 inhibitor NS-398 (10 micro grams/mL) and then exposed to the same dose of LPS. **HO -1** and HO-2(constitutive enzyme) were quantified by RT-PCR-amplification and immunocytochemistry using an **HO- 1** antibody and DAB substrate. A PG-E2 RIA was used to verify COX-2 suppression by the NS-398. Densitometric RT-PCR data was normalized to HO-2 bands (which did not change) and this data was analyzed using ANOVA. N=4 for all conditions. Results: As expected PG-E2 was completely suppressed by the NS-398. Mean control values of **HO-1** were 117+-15 SD densitometric units. These values increased significantly to a mean of 137+-2 after LPS stimulation. These values fell to below control (mean of 110+-12) with P-values of <0.05 between groups with NS-398 exposure. Similar results were seen with immunocytochemistry as indicated by lack of **HO-1** expression after NS-398. Discussion: COX-2 enzymes have a multi-functional role in the inflammatory response after post-ischemic injury. The reduction of **HO- 1** in the face of COX-2 inhibition may have important implications in the control of vascular tone. For example, **HO-1** -mediated increases in endogenous CO and resultant vasodepression, which is a manifestation of endothelial dysfunction, may be prevented with the use of COXibs. Anesthesiology 2003; 99: A669.

=> d 139 ibib abs 90-
YOU HAVE REQUESTED DATA FROM 42 ANSWERS - CONTINUE? Y/(N):y

L39 ANSWER 90 OF 131 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:19431 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400011306
TITLE: COX-2 Inhibition Prevents Heme Oxygenase-1 Expression in Human Microvascular Endothelial Cells.
AUTHOR(S): Armstead, Valerie E. [Reprint Author]; Powell, Garry [Reprint Author]
CORPORATE SOURCE: Anesthesiology, Thomas Jefferson University/Jefferson Med. College, Philadlephia, PA, USA
SOURCE: Anesthesiology Abstracts of Scientific Papers Annual Meeting, (2003) No. 2003, pp. Abstract No. A-669.

http://www.asa-abstracts.com. cd-rom.
Meeting Info.: 2003 Annual Meeting of the American Society of Anesthesiologists. San Francisco, CA, USA. October 11-15, 2003. American Society of Anesthesiologists.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003

AB Introduction:Heme oxygenase-1 (**HO-1**) is a key enzyme in heme catabolism, oxidatively clearing heme to yield biliverdin, iron, and carbon monoxide. Inhibition of heme oxygenase causes an elevation of blood pressure in rats, suggesting that carbon monoxide serves a vasodepressive function. In the present study, we investigated **HO -1** expression in human microvascular endothelial cells in the presence and absence of COX-2 inhibition (Coxibs). Methods: Human adipose microvascular endothelial cells (HADMEC) were cultured and grown to confluence. To elicit a measurable **HO-1** response the HADMEC were stimulated with lipopolysaccharide (LPS) (10 ng/mL). A separate group of cells were pre-treated with the COX-2 inhibitor NS-398 (10 micro grams/mL) and then exposed to the same dose of LPS. **HO -1** and HO-2(constitutive enzyme) were quantified by RT-PCR-amplification and immunocytochemistry using an **HO- 1** antibody and DAB substrate. A PG-E2 RIA was used to verify COX-2 suppression by the NS-398. Densitometric RT-PCR data was normalized to HO-2 bands (which did not change) and this data was analyzed using ANOVA. N=4 for all conditions. Results: As expected PG-E2 was completely suppressed by the NS-398. Mean control values of **HO-1** were 117+-15 SD densitometric units. These values increased significantly to a mean of 137+-2 after LPS stimulation. These values fell to below control (mean of 110+-12) with P-values of <0.05 between groups with NS-398 exposure. Similar results were seen with immunocytochemistry as indicated by lack of **HO-1** expression after NS-398. Discussion: COX-2 enzymes have a multi-functional role in the inflammatory response after post-ischemic injury. The reduction of **HO- 1** in the face of COX-2 inhibition may have important implications in the control of vascular tone. For example, **HO-1** -mediated increases in endogenous CO and resultant vasodepression, which is a manifestation of endothelial dysfunction, may be prevented with the use of COXibs. Anesthesiology 2003; 99: A669.

L39 ANSWER 91 OF 131 MEDLINE on STN DUPLICATE 45
ACCESSION NUMBER: 2002345600 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12087064
TITLE: Ligands of the peroxisome proliferator-activated receptors (PPAR-gamma and PPAR-alpha) reduce myocardial infarct size.
AUTHOR: Wayman Nicole S; Hattori Yoshiyuki; McDonald Michelle C; Mota-Filipe Helder; Cuzzocrea Salvatore; Pisano Babrbara; Chatterjee Prabal K; Thiemermann Christoph
CORPORATE SOURCE: Department of Experimental Medicine and Nephrology, William Harvey Research Institute, St. Bartholomew's and The Royal London School of Medicine and Dentistry, London EC1M 6BQ, UK.
SOURCE: The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2002 Jul) Vol. 16, No. 9, pp. 1027-40.
Journal code: 8804484. E-ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 29 Jun 2002

Last Updated on STN: 18 Mar 2003
Entered Medline: 23 Jul 2002

AB This study was designed to investigate the effects of various chemically distinct activators of PPAR-gamma and PPAR-alpha in a rat model of acute myocardial infarction. Using Northern blot analysis and RT-PCR in samples of rat heart, we document the expression of the mRNA for PPAR-gamma (isoform 1 but not isoform 2) as well as PPAR-beta and PPAR-alpha in freshly isolated cardiac myocytes and cardiac fibroblasts and in the left and right ventricles of the heart. Using a rat model of regional myocardial ischemia and reperfusion (in vivo), we have discovered that various chemically distinct ligands of PPAR-gamma (including the TZDs rosiglitazone, ciglitazone, and pioglitazone, as well as the cyclopentanone **prostaglandins** 15D-PGJ2 and PGA1) cause a substantial reduction of myocardial infarct size in the rat. We demonstrate that two distinct ligands of PPAR-alpha (including clofibrate and WY 14643) also cause a substantial reduction of myocardial infarct size in the rat. The most pronounced reduction in infarct size was observed with the endogenous PPAR-gamma ligand, 15-deoxyDelta12,14- prostagalndin J2 (15D-PGJ2). The mechanisms of the cardioprotective effects of 15D-PGJ2 may include 1) activation of PPAR-alpha, 2) activation of PPAR-gamma, 3) expression of **HO-1**, and 4) inhibition of the activation of NF-kappaB in the ischemic-reperfused heart. Inhibition by 15D-PGJ2 of the activation of NF-kappaB in turn results in a reduction of the 1) expression of inducible nitric oxide synthase and the nitration of proteins by peroxynitrite, 2) formation of the chemokine MCP-1, and 3) expression of the adhesion molecule ICAM-1. We speculate that ligands of PPAR-gamma and PPAR-alpha may be useful in the therapy of conditions associated with ischemia-reperfusion of the heart and other organs. Our findings also imply that TZDs and fibrates may help protect the heart against ischemia-reperfusion injury. This beneficial effect of 15D-PGJ2 was associated with a reduction in the expression of the 1) adhesion molecules ICAM-1 and P-selectin, 2) chemokine macrophage chemotactic protein 1, and 3) inducible isoform of nitric oxide synthase. 15D-PGJ2 reduced the nitration of proteins (immunohistological analysis of nitrotyrosine formation) caused by ischemia-reperfusion, likely due to the generation of peroxynitrite. Not all of the effects of 15D-PGJ2, however, are due to the activation of PPAR-gamma. For instance, exposure of rat cardiac myocytes to 15D-PGJ2, but not to rosiglitazone, results in an up-regulation of the expression of the mRNA for heme-oxygenase-1 (**HO-1**). Taken together, these results provide convincing evidence that several, chemically distinct ligands of PPAR-gamma reduce the tissue necrosis associated with acute myocardial infarction.

L39 ANSWER 92 OF 131 MEDLINE on STN DUPLICATE 46

ACCESSION NUMBER: 2002682430 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12444028
TITLE: Hypoxic induction of cox-2 regulates proliferation of human pulmonary artery smooth muscle cells.
AUTHOR: Yang Xudong; Sheares Karen K K; Davie N; Upton Paul D; Taylor Graham W; Horsley Jo; Wharton John; Morrell Nicholas W
CORPORATE SOURCE: Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospitals, Cambridge, UK.
SOURCE: American journal of respiratory cell and molecular biology, (2002 Dec) Vol. 27, No. 6, pp. 688-96.
Journal code: 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301

ENTRY DATE: Entered STN: 22 Nov 2002
Last Updated on STN: 9 Jan 2003
Entered Medline: 8 Jan 2003

AB Chronic hypoxia-induced pulmonary hypertension results partly from proliferation of smooth muscle cells in small peripheral pulmonary arteries. Therefore, we examined the effect of hypoxia on growth of pulmonary artery smooth muscle cells (PASMCs) from human distal pulmonary arteries. Initial studies identified that serum-induced proliferation of explant-derived PASMCs was inhibited under hypoxic conditions (3-4 kPa in medium). However, selection of hypoxia-stimulated cells was achieved by culturing cells at low density under conditions of prolonged hypoxia (1-2 wk). In hypoxia-inhibited and -stimulated cells, Western blotting revealed hypoxic induction of cyclooxygenase (COX)-2, which was dependent on the activation of p38(MAPK), but not COX-1, inducible nitric oxide synthase (iNOS), or hemoxygenase-1 (**HO-1**). Hypoxic induction of COX-2 was also observed in the media of pulmonary arteries in lung organ culture. Hypoxia induced a 4- to 5-fold increase ($P < 0.001$) in **prostaglandin** (PG)E(2), PGD(2), PGF(2alpha), and 6-keto-PGF(1alpha) release from PASMCs. Hypoxic inhibition of proliferation was attenuated by incubation with indomethacin (10 micro M), or the COX-2 antagonist, NS398 (10 micro M), but not by the COX-1 antagonist, valeryl salicylate (0.5 mM). In conclusion, we have isolated cells from human peripheral pulmonary arteries that are either inhibited or stimulated by culture under hypoxic conditions. In both cell types hypoxia modulates cell proliferation by induction of COX-2 and production of antiproliferative **prostaglandins**. Induction of COX-2 may contribute to the inhibition of hypoxia-induced pulmonary vascular remodeling.

L39 ANSWER 93 OF 131 MEDLINE on STN
ACCESSION NUMBER: 2002150189 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11882623
TITLE: Regulation of cyclooxygenase- and cytochrome p450-derived eicosanoids by heme oxygenase in the rat kidney.
AUTHOR: Botros Fady T; Laniado-Schwartzman Michal; Abraham Nader G
CORPORATE SOURCE: Department of Pharmacology, New York Medical College, Valhalla, NY 10595, USA.
CONTRACT NUMBER: DK56601 (NIDDK)
HL34300 (NHLBI)
SOURCE: Hypertension, (2002 Feb) Vol. 39, No. 2 Pt 2, pp. 639-44.
Journal code: 7906255. E-ISSN: 1524-4563.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 8 Mar 2002
Last Updated on STN: 3 Apr 2002
Entered Medline: 28 Mar 2002

AB Heme oxygenase enzymes (**HO-1** and HO-2) catalyze the conversion of heme to biliverdin, free iron, and carbon monoxide (CO). Heme and products derived from its metabolism potentially influence renal function and blood pressure by affecting the expression and/or activity of hemeproteins, including cytochrome P450 (CYP4A) monooxygenases and cyclooxygenases (COX-1 and COX-2). We studied HO isoform expression and examined the effect of **HO-1** induction by SnCl(2) on CYP4A and COX expression and activity in the rat kidney. **HO- 1** protein levels in kidney tissues from untreated rats were barely detectable, whereas HO-2 protein was expressed in all kidney structures examined and its levels were higher in the outer medulla followed by the inner medulla/papilla and cortex. HO-2 expression along the nephron followed its regional distribution, ie, the

highest levels were detected in the medullary thick ascending limb (mTAL) and inner medullary collecting ducts followed by proximal tubules. SnCl(2) Treatment did not significantly affect HO-2 expression or distribution; however, it markedly increased **HO-1** protein in the inner and outer medulla, specifically, in the inner medullary collecting ducts and mTAL. CYP4A expression and 20-hydroxyeicosatetraenoic acid (20-HETE) synthesis were the highest in the outer medulla followed by the cortex and inner medulla/papilla. SnCl(2) treatment reduced cortical and inner medullary CYP4A protein levels by 60% and 50% and inhibited 20-HETE synthesis by 90% and 60%, respectively. Despite a significant induction of **HO- 1** protein in the outer medulla, CYP4A expression and 20-HETE synthesis were hardly affected. SnCl(2) treatment did not affect COX-1 expression but markedly reduced cortical and medullary COX-2 protein levels. We conclude that HO isoform expression is segmented within the kidney and along the nephron and that treatment with an **HO- 1** inducer suppressed the levels of CYP4A and COX-2 proteins in a tissue-specific manner with concomitant effects on their activity. Such interactions may play an important role in the regulation of renal function.

L39 ANSWER 94 OF 131 MEDLINE on STN DUPLICATE 47
ACCESSION NUMBER: 2002489363 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12230869
TITLE: Effect of **prostaglandin**-J(2) on VEGF synthesis depends on the induction of heme oxygenase-1.
AUTHOR: Jozkowicz Alicja; Huk Ihor; Nigisch Anneliese; Weigel Gunter; Weidinger Franz; Dulak Jozef
CORPORATE SOURCE: Department of Vascular Surgery, AKH, University of Vienna, Austria.. alicia.jozkowicz@akh-wien.ac.at
SOURCE: Antioxidants & redox signaling, (2002 Aug) Vol. 4, No. 4, pp. 577-85.
Journal code: 100888899. ISSN: 1523-0864.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 28 Sep 2002
Last Updated on STN: 22 Mar 2003
Entered Medline: 21 Mar 2003

AB Heme oxygenase-1 (**HO-1**) is an inducible enzyme that degrades heme to carbon monoxide, iron ions, and biliverdin. Its expression can be induced by 15-deoxy-Delta(12,14)**prostaglandin** -J(2) (15d-PGJ(2)), a natural ligand of peroxisome proliferator-activated receptor-gamma transcription factor. In macrophages and vascular smooth muscle cells, 15d-PGJ(2) up-regulates the expression of vascular endothelial growth factor (VEGF), a fundamental regulator of angiogenesis. Here we investigated the involvement of **HO-1** in the 15d-PGJ(2)-mediated regulation of VEGF production by human microvascular endothelial cells (HMEC-1). Resting HMEC-1 released approximately 20 pg/ml VEGF protein after 24 h of incubation. Treatment of cells with 15d-PGJ(2) (1-10 microM) significantly and dose-dependently increased the VEGF promoter activity, mRNA expression, and protein secretion. In the same cells, 15d-PGJ(2) potently induced the expression of **HO- 1** protein that correlated with **HO-1** promoter activity. Activation of **HO-1** with hemin or ectopic overexpression of **HO-1** in HMEC-1 perfectly mimicked the effect of 15d-PGJ(2) and led to increased VEGF production. Importantly, the inhibition of the **HO-1** pathway by tin protoporphyrin-IX significantly reduced the stimulatory effect of 15d-PGJ(2) on VEGF synthesis. Thus, we postulate that the up-regulation of VEGF expression in response to 15d-PGJ(2)in HMEC-1 is mediated by the activation of **HO-1**.

L39 ANSWER 95 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 48
ACCESSION NUMBER: 2002:288916 CAPLUS Full-text
DOCUMENT NUMBER: 137:76302
TITLE: Functional expression of human heme oxygenase-1 (**HO-1**) driven by **HO-1** promoter in vitro and in vivo
AUTHOR(S): Quan, Shuo; Yang, Liming; Shenouda, Sylvia; Jiang, Houli; Balazy, Michael; Schwartzman, Michal L.; Shibahara, Ichiyo; Shinohara, Kousei; Abraham, Nader G.
CORPORATE SOURCE: Department of Pharmacology, New York Medical College, Valhalla, NY, 10595, USA
SOURCE: Journal of Cellular Biochemistry (2002), 85(2), 410-421
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We developed a retrovirus-mediated human heme oxygenase-1 (**HO- 1**) gene expression system and assessed the impact of heme on the inducibility of the **HO-1** gene in rat lung microvessel (RLMV) endothelial cells and in newborn Sprague-Dawley (SD) rats. Overexpression of the **HO-1** gene driven by **HO -1** promoter (HOP) resulted in an increase in **HO- 1** protein and HO activity by 4.8- and 1.3-fold, resp., compared to the viral LTR promoter. The increased **HO-1** gene expression was associated with the enhancement of CO production In cells transduced by HOP-driven **HO-1** gene, there was a decrease in basal cyclooxygenase (COX) activity as measured by PGE2. The degree of **HO-1** expression and consequently, the levels of cellular heme were directly related to COX activity. Supplementation with heme markedly increased PGE2 and cGMP synthesis. In all (6/6) of newborn SD rats injected with retrovirus LSN-HOP-**HO-1**, both **HO-1** and neor transcripts were expressed in tissues. We hypothesize that degree of **HO-1** gene expression resulted in a differential rate of cellular heme-dependent enzyme gene expression, which may play a vital role in maintaining cellular homeostasis.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 96 OF 131 MEDLINE on STN DUPLICATE 49
ACCESSION NUMBER: 2002637971 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12397597
TITLE: Role of human heme oxygenase-1 in attenuating TNF-alpha-mediated inflammation injury in endothelial cells.
AUTHOR: Kushida Taketoshi; Li Volti Giovanni; Quan Shuo; Goodman Alvin; Abraham Nader G
CORPORATE SOURCE: Department of Pharmacology, New York Medical College, Valhalla, New York 10595, USA.
CONTRACT NUMBER: HL-31069 (NHLBI)
HL34300 (NHLBI)
HL55601 (NHLBI)
SOURCE: Journal of cellular biochemistry, (2002) Vol. 87, No. 4, pp. 377-85.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 26 Oct 2002
Last Updated on STN: 28 Jun 2003
Entered Medline: 27 Jun 2003

AB Heme oxygenase (HO) is the rate-limiting enzyme in the formation of bilirubin, an antioxidant, and carbon monoxide (CO), a cell cycle modulator and a vasodilator. Cyclooxygenase (COX) is a hemeprotein that catalyzes the conversion of arachidonic acid (AA) to various prostanoids, which play an important role in the regulation of vascular endothelial function in normal and disease states. The influence of suppression or overexpression of HO isoforms on COX expression and synthesis of prostanoids is of considerable physiological importance. Consequently, the goal of the present study was to determine whether the heme-HO system regulates COX enzyme expression and activity in vascular endothelial cells in the absence and presence of TNF-alpha (100 ng/ml). Endothelial cells stably transfected with the retrovirus containing the human **HO- 1** gene exhibited a several-fold increase in **HO-1** protein levels, which was accompanied by an increase in HO activity and a marked decrease in PGE(2) and 6-keto PGF(1alpha) levels. We also assessed the effect of retrovirus-mediated **HO-1** gene transfer in the sense and antisense orientation on **HO-1** expression and cell cycle progression in human endothelial cells. The levels of CO and HO activity were increased in cells transduced with the **HO-1** sense and were greatly suppressed in cells transduced with **HO-1** antisense as compared to control sham-transduced cells ($P < 0.05$). The percentage of the G(1)-phase in cells transduced with **HO-1** significantly increased (41.4% +/- 9.1) compared with control endothelial cells (34.8% +/- 4.9). We measured COX activity by determining the levels of PGI(2) and PGE(2). The levels of PGI(2) decreased in cells transduced with **HO- 1** sense and increased in cells transduced with **HO- 1** in antisense orientation. The expression of p27 was also studied and showed a marked decrease in cells transduced with **HO -1** sense and a marked increase in the **HO-1** antisense transduced cells. Cell cycle analysis of endothelial cell DNA distributions indicated that the TNF-alpha-induced decrease in the proportion of G(1)-phase cells and increase in apoptotic cells in control cultures could be abrogated by transfection with **HO-1** in the sense orientation. Tin mesoporphyrin (SnMP) reversed the protective effect of **HO-1**. These results demonstrate that overexpressing **HO-1** mitigated the TNF-alpha-mediated changes in cell cycle progression and apoptosis, perhaps by a decrease in the levels of COX activity. Copyright 2002 Wiley-Liss, Inc.

L39 ANSWER 97 OF 131 MEDLINE on STN DUPLICATE 50
ACCESSION NUMBER: 2002364490 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12112002
TITLE: Nitric oxide and **prostaglandin** E2 participate in lipopolysaccharide/interferon-gamma-induced heme oxygenase 1 and prevent RAW264.7 macrophages from UV-irradiation-induced cell death.
AUTHOR: Chen Yen-Chou; Shen Shing-Chuan; Lee Woan-Ruoh; Lin Hui-Yi; Ko Ching-Huai; Lee Tony J F
CORPORATE SOURCE: Graduate Institute of Pharmacognosy Science, Taipei Medical University, Taiwan.. yc3270@tmu.edu.tw
CONTRACT NUMBER: HL 47574 (NHLBI)
HL27763 (NHLBI)
SOURCE: Journal of cellular biochemistry, (2002) Vol. 86, No. 2, pp. 331-9.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 12 Jul 2002
Last Updated on STN: 18 Dec 2002
Entered Medline: 13 Dec 2002

AB Induction of heme oxygenase (**HO**)-**1** during inflammation has been demonstrated in many cell types, but the contribution of inflammatory molecules nitric oxide (NO) and **prostaglandin** E(2) (PGE(2)) has remained unresolved. Here we show that NO donors including sodium nitroprusside (SNP) and spermine nonoate (SP-NO), and PGE(2) significantly stimulate **HO-1** expression in RAW264.7 macrophages, associated with alternative induction on NO and PGE(2) in medium, respectively. NO donors also show the inductive effect on cyclo-oxygenase 2 protein and PGE(2) production. In the presence of lipopolysaccharide and interferon-gamma (LPS/IFN-gamma), **HO- 1** protein was induced slightly but significantly, and SNP, SP-NO, and PGE(2) enhanced **HO-1** protein induced by LPS/IFN-gamma. L-Arginine analogs N-nitro-L-arginine methyl ester (L-NAME) and N-nitro-L-arginine (NLA) significantly block **HO- 1** protein induced by LPS/IFN-gamma associated with a decrease in NO (not PGE(2)) production. And, NSAIDs aspirin and diclofenase dose dependently inhibited LPS/IFN-gamma-induced **HO-1** protein accompanied by suppression of PGE(2) (not NO) production. PD98059 (a specific inhibitor of MEKK), but not SB203580 (a specific inhibitor of p38 kinase), attenuated PGE(2) (not SP-NO) induced **HO-1** protein. Under UVC (100 J/m(2)) and UVB (50 J/m(2)) irradiation, PGE(2) or SP-NO treatment prevents cells from UVC or UVB-induced cell death, and **HO-1** inhibitor tin protoporphyrin (SnPP) reverses the preventive effects of PGE(2) and SP-NO. The protective activity induced by PGE(2) on UVC or UVB irradiation-induced cell death was blocked by MAPK inhibitor PD98059 (not SB203580). These results demonstrated that inflammatory molecules NO and PGE(2) were potent inducers of **HO- 1** gene, and protected cells from UV-irradiation-induced cell death through **HO-1** induction.

L39 ANSWER 98 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:670705 CAPLUS Full-text
DOCUMENT NUMBER: 137:349918
TITLE: Induction of heme oxygenase in guinea-pig stomach: Roles in contraction and in single muscle cell ionic currents
AUTHOR(S): Kadinov, B.; Itzev, D.; Gagov, H.; Christova, T.; Bolton, T. B.; Duridanova, D.
CORPORATE SOURCE: Institute of Physiology, Bulgarian Academy of Sciences, Sofia, 1113, Bulg.
SOURCE: Acta Physiologica Scandinavica (2002), 175(4), 297-313
CODEN: APSCAX; ISSN: 0001-6772
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of heme oxygenase (HO) reaction products in modulation of stomach fundus excitability was studied. The presence of constitutive HO-2 isoenzyme was verified in myenteric ganglia by immunohistochem. The role of inducible **HO-1** isoenzyme was investigated after in vivo treatment of animals with CoCl2 (80 mg/kg b.w) injected s.c. 24 h before they were killed. This treatment resulted in increased production of bilirubin and pos. staining for the inducible **HO-1** isoform in stomach smooth muscle and vast induction in the liver. In both control and treated animals, hemin, applied to the bath as a substrate of HO caused a significant decrease in **prostaglandin** F2α-induced tone, and ameliorated the relaxatory response of the fundic strips to elec.

field stimulation. Both effects were antagonized by Sn-protoporphyrin IX, a competitive HO inhibitor, and were found to be neuronally dependent. In single freshly isolated smooth muscle cells from control animals, hemin caused a concentration-dependent increase in the whole cell K+ currents, which was not affected by Sn-protoporphyrin IX, cGMP-dependent protein kinase, or guanylyl cyclase antagonists, but was reversed by various antioxidants and abolished by an NO scavenger. In cells from treated animals, the K+ current-increasing effect of hemin did not depend on the presence of antioxidants, but was abolished by protein kinase G and guanylyl cyclase inhibitors, depletors of intracellular Ca2+ pools, or Sn-protoporphyrin IX. Biliverdin did not affect contraction or ionic currents. Thus, this is the 1st study demonstrating that HO is an inducible enzyme in guinea pigs, which exerts a modulatory role on gastric smooth muscle excitability via CO production

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 99 OF 131 MEDLINE on STN DUPLICATE 51

ACCESSION NUMBER: 2002314547 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12056503
TITLE: Bradykinin as a major endogenous regulator of endothelial function.
AUTHOR: Gryglewski Ryszard J; Uracz Wojciech; Chlopicki Stefan; Marcinkiewicz Ewa
CORPORATE SOURCE: Jagiellonian University, Cracow, Poland.. mfgrygle@kinga.cyf-kr.edu.pl
SOURCE: Pediatric pathology & molecular medicine, (2002 May-Jun) Vol. 21, No. 3, pp. 279-90.
Journal code: 100885435. ISSN: 1522-7952.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 12 Jun 2002
Last Updated on STN: 17 Dec 2002
Entered Medline: 4 Dec 2002

AB Healthy vascular endothelium is a powerful generator of nitric oxide (NO), prostacyclin (PGI2), **prostaglandin** E2 (PGE2), and plasminogen activator (t-PA). These endothelial products protect vascular wall against aggression from activated blood platelets and leukocytes. In particular they protect against thrombosis, promote thrombolysis, maintain tissue perfusion, and inhibit remodeling of vascular and cardiac walls. Endothelial dysfunction appears on one hand as suppression in the release of the above mediators, and on the other as deleterious discharge of **prostaglandin** endoperoxides (PGH2, PGG2), superoxide anion O2-, peroxynitrite (ONOO-), and plasminogen activator inhibitor (PAI-1). Our data point to endothelial bradykinin (Bk) as a trigger for protective endothelial mechanisms. In cultured endothelial cells (CEC) Bk through kinin B2 receptors raised in a concentration-dependent manner (1pM-10 nM) free cytoplasmic calcium ions [Ca2+]i. This rise was accompanied by the release of NO as quantified by a porphyrinic sensor. Other endothelial agonists were weaker-stimulators of [Ca2+]i than Bk. In vivo we analyed the effects of exogenous Bk and of amplifiers of endogenous Bk, such as perindopril and quinapril ("tissue type" angiotensin converting enzyme inhibitors, ACE-I) on endothelial function using our original thrombolytic bioassay and EIA assays for 6-keto-PGF1alpha and t-PA antigen. A major difference found between exogenuous Bk and endogenous Bk (that rendered by "tissue ACE-I") was a) prolonged thrombolytic action (> 4h) of quinapril or perindopril. Moreover, only exogenous Bk evoked an immediate and profound hypotensive action. In vivo, Bk-induced thrombolysis was B2 kinin receptor-

dependent, PGI2-mediated. The unexpected action of Bk came to light in CEC. Then appeared incubated for 4 h increased expression of mRNAs for haemoxygenase (**HO-1**), cyclooxygenase 2 (COX-2), **prostaglandin** E synthase (PGE-S), but hardly for nitric oxide synthase 2(NOS-2). We hypothesize that a network of interactions of Bk-induced enzymes may constitute a delayed phase of Bk effects in the endothelium, whereas the primary phase would be activation by BK of [Ca2+]i-dependent constitutive endothelial enzymes. In blood-perfused rat endotoxemic lungs, NO is the most eminent cytoprotective mediator. Summing up, in peripheral circulation endogenous Bk is the most efficient activator of protective endothelial function. Thrombolytic action of "tissue-type" ACE-Is relies on receptor B-2-mediated, [Ca2+]i-dependent release of PGI2. Bk also may act as a "microcytokine" by inducing mRNAs for **HO-1**, COX-2, or PGE-S. Activation of **HO -1** may lead to a deficiency in intracellular heme required as a cofactor for both COX and NOS. This network of interactions triggered by Bk call for further studies.

L39 ANSWER 100 OF 131 MEDLINE on STN DUPLICATE 52
ACCESSION NUMBER: 2002266513 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12006176
TITLE: Activation of the mouse heme oxygenase-1 gene by 15-deoxy-Delta(12,14)-**prostaglandin** J(2) is mediated by the stress response elements and transcription factor Nrf2.
AUTHOR: Gong Pengfei; Stewart Daniel; Hu Bin; Li Ning; Cook Julia; Nel Andre; Alam Jawed
CORPORATE SOURCE: Department of Molecular Genetics, Alton Ochsner Medical Foundation, New Orleans, LA 70121, USA.
CONTRACT NUMBER: AI-50495 (NIAID)
DK-43135 (NIDDK)
ES-10553 (NIEHS)
SOURCE: Antioxidants & redox signaling, (2002 Apr) Vol. 4, No. 2, pp. 249-57.
Journal code: 100888899. ISSN: 1523-0864.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 14 May 2002
Last Updated on STN: 14 Sep 2002
Entered Medline: 13 Sep 2002

AB The mechanism of heme oxygenase-1 (**ho-1**) gene activation by 15-deoxy-Delta(12,14)-**prostaglandin** J(2) (15d-PGJ(2)) was examined. 15d-PGJ(2) stimulated expression of **HO -1** mRNA and protein and of a mouse **ho-1** gene promoter/luciferase fusion construct (HO15luc) in a dose-dependent manner in mouse hepatoma (Hepa) cells. HO15luc expression was not effected by troglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR-gamma) ligand, but induction by 15d-PGJ(2) was abrogated by the antioxidant N-acetylcysteine. The primary 15d-PGJ(2) responsive sequences were localized to a 5' distal enhancer (E1) and identified as the stress-response element, previously shown to mediate **ho- 1** activation by several agents, including heme and heavy metals. Treatment of Hepa cells with 15d-PGJ(2) stimulated stress-response element-binding activity as judged by electrophoretic mobility shift assays. Antibody "supershift" experiments identified NF-E2 related factor 2 (Nrf2), but not Fos, Jun, or activating transcription factor/cyclic AMP response element binding protein transcription factors, within the 15d-PGJ(2)-induced complexes. Similarly, a dominant-negative mutant of Nrf2, but not of c-Jun or c-Fos, abrogated 15d-PGJ(2)-stimulated E1 transcription activity.

Finally, prior induction of **HO- 1** in RAW264.7 mouse macrophages by 15d-PGJ(2) attenuated cell death caused by diesel exhaust particle extracts. These results demonstrate that induction of mouse **HO-1** expression by 15d-PGJ(2) is independent of PPAR-gamma but dependent on oxidative stress, is regulated by the oxidative stress-activated transcription factor Nrf2, and provides cytoprotective activity.

L39 ANSWER 101 OF 131 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:323415 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200323415
TITLE: Oligosaccharides of agar show strong anti-inflammatory activities: By inducing hemeoxygenase-I (**HO-1**); suppressing the expression of inducible nitrogen oxide synthase (iNOS) and TNF-alpha.
AUTHOR(S): Sagawa, Hiroaki [Reprint author]; Enoki, Tatsuji; Mineno, Junichi; Kato, Ikunoshin
CORPORATE SOURCE: Biotechnology Research Laboratories, Takara Shuzo Co., Ltd., Seta 3-4-1, Otsu, Shiga, 520-2193, Japan
SOURCE: FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A223. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jun 2002
Last Updated on STN: 5 Jun 2002

AB Agar from red algae is one of the most popular polysaccharides that are consumed in Japan as a health-food for longtime. Agarose is the main constituent of agar composed of the alternating residues of 3-O-linked beta-D-galactopyranose (Gal) and 4-0-linked 3,6-anhydro-alpha-L- galactopyranose (AhGal). Acid hydrolysis of 1-3-alpha-linkage of agarose produces agaro-oligosaccharides (A-oligo) having AhGal at their reducing end. We previously reported that under mild alkaline condition, A-oligo is converted into an active agent, DGE (L-glycero-1,5-epoxy alpha beta, 6-dihydroxy-cis-hex-3-en-2-one) that show anti-inflammatory activities by inhibiting the production of nitrogen oxide and **prostaglandin** E2. Thus we examined the effects of DGE on the gene expression profile in neutrophil like cells utilizing microbeads array and DNA microarray technologies. We found that A-oligo induced the expression of **HO -1** that produces a Carbon mono oxide (CO) that suppresses the expression of the inflammatory cytokines: TNFalpha; IL-1beta; MIP-1beta. **HO-1** also produces iron that inhibits the expression of iNOS resulting in decrement of NO production. We conclude that the anti-inflammatory activities of A-oligo are triggered by induction of **HO-1**.

L39 ANSWER 102 OF 131 MEDLINE on STN DUPLICATE 53

ACCESSION NUMBER: 2002003820 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11752115
TITLE: Regulation of cyclooxygenase by the heme-heme oxygenase system in microvessel endothelial cells.
AUTHOR: Haider Asifa; Olszanecki Rafal; Gryglewski Richard; Schwartzman Michal L; Lianos Elias; Kappas Attallah; Nasjletti Alberto; Abraham Nader G
CORPORATE SOURCE: New York Medical College, Department of Pharmacology, Valhalla, New York 10595, USA.

CONTRACT NUMBER: DK56601 (NIDDK)
HL34300 (NHLBI)
SOURCE: The Journal of pharmacology and experimental therapeutics, (2002 Jan) Vol. 300, No. 1, pp. 188-94.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 2 Jan 2002
Last Updated on STN: 28 Jan 2002
Entered Medline: 24 Jan 2002

AB Heme oxygenase (HO) is a microsomal enzyme that oxidatively cleaves heme to form biliverdin, with the release of iron and carbon monoxide (CO). HO not only controls the availability of heme for the synthesis of heme proteins but also is responsible for the generation of CO, which binds to the heme moiety of heme proteins thus affecting their enzymatic activity. Cyclooxygenase (COX) is a heme protein that catalyzes the conversion of arachidonic acid to **prostaglandin** H(2), the precursor of prostanoids that participate in the regulation of vascular function. The goal of the present study was to determine whether the heme-HO system regulates COX enzyme expression and activity in vascular endothelial cells. Endothelial cells stably transfected with the human **HO- 1** gene exhibited a severalfold increase in human **HO- 1** mRNA levels, which was accompanied by an increase in HO activity and a marked decrease in **prostaglandin** (PG) E(2) and 6-keto-PGF(1alpha) levels. Exposure of cells to CoCl(2), an inducer of **HO-1** gene expression, resulted in increases in **HO-1** protein levels and HO activity. The increase in HO activity was associated with a subsequent decrease in COX activity, which returned to normal levels following normalization of HO activity. The addition of heme resulted in an increase in COX activity with an increase in PGE(2) and 6-keto-PGF(1alpha) levels. The degree of **HO- 1** expression and, consequently, the level of cellular heme, were directly related to COX activity. These results demonstrate that the heme-HO system can function as a cellular regulator of the expression of vascular COX, thus influencing the generation of prostanoids, PGE(2) and PGI(2), known to play a role in vascular homeostasis.

L39 ANSWER 103 OF 131 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:323293 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200323293
TITLE: Regulatory role of heme oxygenase gene expression on heme dependent enzymes in endothelial cells using retroviral constructs.
AUTHOR(S): Ahmed, Fareeda [Reprint author]; Abraham, Nader; Yang, Liming
CORPORATE SOURCE: New York Medical College, Valhalla, NY, 10595, USA
SOURCE: FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A174. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jun 2002

Last Updated on STN: 5 Jun 2002

AB We developed a retrovirus-mediated human heme oxygenase (**HO- 1**) gene expression system and assessed the impact of heme on the inducibility of the **HO-1** gene in rat lung microvessel (RLMV) endothelial cells and heme dependent enzymes activities. Overexpression of the **HO-1** gnee resulted in an increase in **HO-1** protein and HO activity by 4.8- and 1.3-fold, respectively, compared to the cells transfected by empty viral vector. The increased **HO-1** gene expression was associated with the enhancement of CO production. In cells transduced by HOP-driven **HO-1** gene, there was a decrease in basal cyclooxygenase (COX) activity as measured by PGE2. The degree of **HO-1** expression and, consequently, the levels of cellular heme were directly related to COX activity. Supplementation with heme markedly increased PGE2 and cGMP synthesis. Carbon monoxide (CO) production in overexpression **HO-1** cells after heme treatment was increased (159%) compared to nontransduced cells. The increased **HO-1** gene expression was associated with the enhancement of CO production. In cells transduced by **HO- 1** gene, there was a decrease in basal cyclooxygenase (COX) activity as measured by PGE2. HO-2 protein level did not change. We hypothesize that the degree of **HO-1** gene expression resulted in a differential rate o fcellular heme-dependent enzyme gene expression, and modulating cyclooxygenase and soluble guanylate cyclase activities, which may play a vital role in maintaining hemostasis.

L39 ANSWER 104 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:835244 CAPLUS Full-text
DOCUMENT NUMBER: 138:120659
TITLE: Behavior of **HO-1**-N-1, buccal mucosa carcinoma derived cells, on [Ca2+]i responses to stimulants
AUTHOR(S): Arai, Takafumi; Matsumoto, Hiroko; Akimoto, Yoshiaki; Nishimura, Hitoshi; Ono, Makiko; Fujii, Akira
CORPORATE SOURCE: Department of Pharmacology, Nihon University School of Dentistry at Matsudo, Chiba, 271-8587, Japan
SOURCE: Journal of Oral Science (2002), 44(2), 103-108
CODEN: JORSF3; ISSN: 1343-4934
PUBLISHER: Nihon University School of Dentistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Buccal mucosa carcinoma-derived cell line, **HO-1**-N-1, epithelial-like cells, was obtained in order to investigate the characteristics of oral cancer cells and examine the [Ca2+]i response to stimulants, such as bradykinin (BK), histamine (HIST), thapsigargin (TG), epidermal growth factor (EGF) and transforming growth factor α (TGFα). Intracellular Ca2+ influx was observed by all stimulants that enhanced the [Ca2+]i response. However, intracellular Ca2+ release was not observed in response to growth factors. The [Ca2+]i response of BK was inhibited by a BKB2 antagonist, and the response to HIST (1 mM) was completely inhibited by an H1 antagonist, in the presence and absence of extracellular Ca2.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 105 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 54
ACCESSION NUMBER: 2003:591909 CAPLUS Full-text
DOCUMENT NUMBER: 139:228022
TITLE: Gene expression of nitric oxide synthase and heme oxygenase in placental villi during pregnancy with and without intrauterine growth restriction
AUTHOR(S): Muta, Kunio; Masuzaki, Hideaki; Urata, Yoshishige; Goto, Shinji; Ishimaru, Tadayuki; Kondo, Takahito
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Nagasaki

University School of Medicine, Nagasaki, 852-8501, Japan

SOURCE: Journal of Clinical Biochemistry and Nutrition (2002), 32, 11-21
CODEN: JCBNER; ISSN: 0912-0009

PUBLISHER: Gakkai Shuppan Senta

DOCUMENT TYPE: Journal

LANGUAGE: English

AB It is commonly accepted that the intrauterine growth restriction (IUGR) is correlated with an impairment of utero-placental blood flow. This blood flow is regulated by **prostaglandins** and NO, which regulate vascular tone in placental villi. The factors that regulate utero-placental blood flow play different functions independently, and their functions differ according to the gestational stage. To evaluate the influence of NO and CO on the feto-maternal circulation, the authors quantified endothelial nitric oxide synthase (eNOS) and heme oxygenase (HO) type 1 (**HO-1**) mRNAs in the placental villi. Forty-three placental samples were studied. Both eNOS and **HO- 1** mRNAs were measured by Northern blot hybridization. The eNOS mRNA expression in the 1st trimester (relative intensity, 3.741 ± 0.679, mean ± SEM) was higher than that after the 1st trimester (0.500 ± 0.038, $p < 0.0001$). **HO-1** mRNA expression in the 3rd trimester was higher than that before the 3rd trimester (2.648 ± 0.409 and 1.122 ± 0.182, resp., $p < 0.005$). There were no differences in the expression of eNOS and **HO-1** mRNAs between pregnancies with or without IUGR. The independent expression of eNOS and **HO-1** mRNAs suggests that eNOS is important in placentation at early gestation, whereas **HO-1** is important in maintenance of pregnancy for the term.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 106 OF 131 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:322600 BIOSIS Full-text

DOCUMENT NUMBER: PREV200200322600

TITLE: The Nrf2 transcription factor mediates induction of the heme oxygenase-1 gene by 15-deoxy-DELTA12,14-**prostaglandin** J2.

AUTHOR(S): Stewart, Daniel [Reprint author]; Gong, Pengfei [Reprint author]; Hu, Bin [Reprint author]; Li, Ning; Cook, Julia L. [Reprint author]; Nel, Andre [Reprint author]; Alam, Jawed [Reprint author]

CORPORATE SOURCE: Ochsner Clinic Foundation, 1516 Jeffefferson highway, New Orleans, LA, 70121, USA

SOURCE: FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A10. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 5 Jun 2002
Last Updated on STN: 5 Jun 2002

AB The mechanism of heme oxygenase-1 (**ho-1**) gene activation by 15-deoxy-DELTA 12,14-**prostaglandin** J2 (15d-PGJ2) was examined. 15d-PGJ2 stimulated expression of **HO-1** mRNA and activity of the **ho-1** gene promoter in a dose-dependent manner in mouse hepatoma cells. Promoter activity was not effected by troglitazone, a PPAR-gamma ligand, but induction by 15d-PGJ2 was abrogated by the antioxidant N-acetyl cysteine. The primary 15d-PGJ2 responsive sequences were localized to a 5' distal enhancer (E1) and identified as the stress-response

elements (StREs). Treatment of Hepa cells with 15d-PGJ2 stimulated StRE-binding activity and antibody "supershift" experiments identified Nrf2, but not Fos, Jun or ATF/CREB transcription factors, within the DNA-protein complexes. Similarly, a dominant mutant of Nrf2, but not of c-Jun or c-Fos, abrogated 15d-PGJ2-stimulated E1 transcription activity. Finally, prior induction of **HO-1** in macrophage cells by 15d-PGJ2 attenuated cell death caused by diesel exhaust particle extracts. These results demonstrate that induction of **HO-1** by 15d-PGJ2 is independent of PPAR-gamma but dependent on oxidative stress, is regulated by the stress-activated factor Nrf2, and provides cytoprotective activity.

L39 ANSWER 107 OF 131 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:31677 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400033721
TITLE: 15-Deoxy-delta 12, 14-**Prostaglandin** J2 inhibits proliferation of human myofibroblasts by a pathway involving heme-oxygenase-1.
AUTHOR(S): Li, Liying [Reprint Author]; Mallat, Ariane [Reprint Author]; Lotersztajn, Sophie [Reprint Author]
CORPORATE SOURCE: INSERM U99, Hopital Henri Mondor, Creteil, France
SOURCE: Journal of Hepatology, (April 2002) Vol. 36, No. Supplement 1, pp. 9-10. print.
Meeting Info.: Biennial Meeting of the International Association for the Study of the Liver. Madrid, Spain. April 15-16, 2002. European Association for the Study of the Liver; International Association for the Study of the Liver.
ISSN: 0168-8278 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jan 2004
Last Updated on STN: 7 Jan 2004

L39 ANSWER 108 OF 131 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:531235 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200531235
TITLE: Regulation of heme oxygenase-1 and heme trafficking in Caco-2 cells.
AUTHOR(S): Uc, Aliye [Reprint author]; McCormick, Michael L. [Reprint author]; Stokes, John B. [Reprint author]; Britigan, Bradley E. [Reprint author]
CORPORATE SOURCE: Iowa City, IA, USA
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A.541. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 2002
Last Updated on STN: 5 Dec 2002

L39 ANSWER 109 OF 131 MEDLINE on STN

ACCESSION NUMBER: 2001645682 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 11698254
TITLE: Cerebral vascular endothelial heme oxygenase: expression, localization, and activation by glutamate.
AUTHOR: Parfenova H; Neff R A 3rd; Alonso J S; Shlopov B V; Jamal C N; Sarkisova S A; Leffler C W
CORPORATE SOURCE: Laboratory for Research in Neonatal Physiology, Department of Physiology, University of Tennessee Health Science Center, Memphis, Tennessee 38163, USA.. hparf@physio1.utmem.edu
SOURCE: American journal of physiology. Cell physiology, (2001 Dec) Vol. 281, No. 6, pp. C1954-63.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 8 Nov 2001
Last Updated on STN: 23 Jan 2002
Entered Medline: 27 Dec 2001

AB Endogenous carbon monoxide (CO) contributes to vasodilator responses of cerebral microvessels in newborn pigs. We investigated the expression, intracellular localization, and activity of heme oxygenase (HO), the key enzyme in CO production, in quiescent cerebral microvascular endothelial cells (CMVEC) from newborn pigs. **HO-1** and HO-2 isoforms were detected by RT-PCR, immunoblotting, and immunofluorescence. **HO-1** and HO-2 are membrane-bound proteins that have a strong preference for the nuclear envelope and perinuclear area of the cytoplasm. Betamethasone (10(-6) to 10(-4) M for 48 h) was associated with upregulation of HO-2 protein by approximately 50% and inhibition of Cox-2 but did not alter **HO-1** or endothelial nitric oxide synthase expression in CMVEC. In vivo betamethasone treatment of newborn pigs (0.2 and 5.0 mg/kg im for 48 h) upregulated HO-2 in cerebral microvessels by 30-60%. HO activity as (14)CO production from [(14)C]glycine-labeled endogenous heme was inhibited by chromium mesoporphyrin (10(-6) to 10(-4) M). L-Glutamate (0.3-1.0 mM) stimulated HO activity 1.5-fold. High-affinity specific binding sites for L-[(3)H]glutamate suggestive of the glutamate receptors were detected in CMVEC. Altogether, these data suggest that, in cerebral circulation of newborn pigs, endothelium-derived CO may contribute to basal vascular tone and to responses that involve glutamate receptor activation.

L39 ANSWER 110 OF 131 MEDLINE on STN DUPLICATE 55
ACCESSION NUMBER: 2001402970 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11454666
TITLE: Modulation of haem oxygenase-1 expression by nitric oxide and leukotrienes in zymosan-activated macrophages.
AUTHOR: Vicente A M; Guillen M I; Alcaraz M J
CORPORATE SOURCE: Department of Pharmacology, University of Valencia, 46100 Burjasot, Valencia, Spain.
SOURCE: British journal of pharmacology, (2001 Jul) Vol. 133, No. 6, pp. 920-6..
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109

ENTRY DATE: Entered STN: 10 Sep 2001
Last Updated on STN: 19 Dec 2002
Entered Medline: 6 Sep 2001

AB Phagocytosis of unopsonized zymosan by RAW 264.7 macrophages upregulated protein expression of haem oxygenase-1 (**HO-1**), inducible nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX-2) in a time- and concentration-dependent manner. In the presence of zymosan, exogenous **prostaglandin** E(2) (PGE(2)) did not exert significant effects on the expression of these three enzymes. In contrast, exogenous leukotriene B(4) (LTB(4)) and LTC(4) in the nanomolar range inhibited **HO-1** and iNOS expression, as well as nitrite accumulation. The COX inhibitors indomethacin and NS398 weakly inhibited **HO-1** expression but had no effect on iNOS and COX-2 expression or nitrite. In contrast, the 5-lipoxygenase (5-LO) inhibitor ZM 230,487 significantly decreased **HO-1**, iNOS and nitrite, which were not affected by zileuton. Dexamethasone showed an inhibitory effect on **HO-1** expression induced by zymosan. ZM 230,487 but not zileuton, inhibited the shift due to nuclear factor-kappaB (NF-kappaB), whereas they did not modify activator protein-1 (AP-1) binding. Our results suggest that inhibition of NF-kappaB binding could mediate the effects of ZM 230,487 on the modulation of **HO- 1** and iNOS protein expression. NOS inhibition by L-N(G)-nitroarginine methyl ester (L-NAME) or 1400 W abolished nitrite production and strongly reduced **HO-1** expression. These results show an induction of **HO-1** protein expression by zymosan phagocytosis in macrophages, with a positive modulatory role for endogenous NO and a negative regulation by exogenous LTs, likely dependent on the reduction of iNOS expression and NO production.

L39 ANSWER 111 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:679027 CAPLUS Full-text
DOCUMENT NUMBER: 136:230150
TITLE: "Haemoxygenase-1 induction and exhaled markers of oxidative stress in lung diseases", summary of the ERS research seminar in Budapest, Hungary, September, 1999
AUTHOR(S): Horvath, I.; MacNee, W.; Kelly, F. J.; Dekhuijzen, P. N. R.; Phillips, M.; Doring, G.; Choi, A. M. K.; Yamaya, M.; Bach, F. H.; Willis, D.; Donnelly, L. E.; Chung, K. F.; Barnes, P. J.
CORPORATE SOURCE: Dept of Pathophysiology, National Koranyi Institute for Putmonology, Budapest, H-1529, Hung.
SOURCE: European Respiratory Journal (2001), 18(2), 420-430
CODEN: ERJOEI; ISSN: 0903-1936
PUBLISHER: European Respiratory Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. In recent years, there has been increasing interest in noninvasive monitoring of airway inflammation and oxidative stress. Several volatile and nonvolatile substances can be measured in exhaled breath and have been suggested as potential biomarkers of these events. Exhaled gases, including carbon monoxide (CO), alkanes (ethane, pentane), and substances measured in breath condensate, such as hydrogen peroxide (H2O2) and isoprostanes were all suggested as potential markers of oxidative stress in the lung. A European Respiratory Society (ERS) International Research Seminar entitled "Haemoxygenase-1 induction and exhaled markers of oxidative stress in lung diseases" was organized by the Airway Regulation and Provocation Group of the Clin. Allergy and Immunol. Assembly in Budapest, Hungary in Sept., 1999 to integrate the latest knowledge on these issues and accelerate further improvement in this area. During this 2-day event several issues were raised about: the use and standardization of measurements in exhaled breath; problems of measuring expired H2O2 and other mediators in breath condensate; role and regulation of heme oxygenase (**HO**)-1 in the lung; and conditions and factors

influencing exhaled CO. This report is a summary of the main presentations at the seminar, together with the current areas of research in this rapidly expanding field.

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 112 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:678879 CAPLUS Full-text
DOCUMENT NUMBER: 135:339825
TITLE: Bradykinin as a strong inducer of COX-2 mRNA and a weak inducer of NOS-2 mRNA in cultured endothelial cells from human umbilical vein
AUTHOR(S): Uracz, Danuta; Uracz, Wojciech; Gryglewski, Ryszard J.
CORPORATE SOURCE: Chair of Pharmacology, Jagiellonian University Medical College, Krakow, 31-531, Pol.
SOURCE: NATO Science Series, Series A: Life Sciences (2001), 317(Nitric Oxide), 207-209
CODEN: NASAF2; ISSN: 1387-6686
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exogenous bradykinin stimulates endothelial release of EDRF(NO), prostacyclin and endothelium derived hyperpolarizing factor (EDHF). In humans, endogenous bradykinin controls vasomotor function of coronary circulation via stimulation of kinin B2 receptors. Bradykinin is inactivated by the kininase II function within angiotensin converting enzyme (ACE). Therefore, accumulation of bradykinin may explain some of the endothelium-dependent vascular effects of ACE inhibitors (ACE-I). The authors demonstrated elsewhere that bradykinin as compared to ADP, acetylcholine, adrenaline, 5-hydroxytryptamine or even calcium ionophore is the most potent agent in rising free cytosolic calcium level (Ca2+)i and NO release from cultured bovine aortic endothelial cells (BAEC). Apart from its classical role of a tissue hormone, bradykinin may act as a growth factor, and this is why it may behave as a cytokine. For instance, bradykinin was reported to induce COX-2 in cultured human airway smooth muscles cells and in HUVEC. Because of its low mol. weight bradykinin is not usually classified as a cytokine or a growth factor. In this respect "minicytokine" may be a more appropriate name for bradykinin. Indeed, the authors describe here an example of the minicytokine type action of bradykinin. Four hours incubation of cultured human umbilical vein endothelial cells (HUVEC) with bradykinin (10 nM!) resulted in induction of the mRNAs for hemooxygenase 1-(**HO-1**), cyclooxygenase 2-(COX-2), **prostaglandin** E synthase (PGE-S) and, insignificantly, for nitric oxide synthase 2 (NOS-2).
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 113 OF 131 MEDLINE on STN
ACCESSION NUMBER: 2001200078 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11287117
TITLE: Heme oxygenase-1 induction by nitric oxide in RAW 264.7 macrophages is upregulated by a cyclo-oxygenase-2 inhibitor.
AUTHOR: Alcaraz M J; Habib A; Creminon C; Vicente A M; Lebret M; Levy-Toledano S; Maclouf J
CORPORATE SOURCE: Department of Pharmacology, University of Valencia, Spain.. maria.j.alcarez@uv.es
SOURCE: Biochimica et biophysica acta, (2001 Apr 3) Vol. 1526, No. 1, pp. 13-6.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 17 May 2001
Last Updated on STN: 17 May 2001
Entered Medline: 10 May 2001

AB Unstimulated RAW 264.7 macrophages express negligible heme oxygenase-1 (**HO-1**) protein but incubation with the nitric oxide (NO) donor spermine nonoate (SPNO) induced **HO-1** and weakly cyclo-oxygenase-2 (COX-2) protein. This effect was potentiated by coincubation with the COX-2 selective inhibitor, SC58125. Cells incubated with SPNO showed a strong increase in **HO-1** mRNA levels after 4 h with a significant potentiation in the presence of SC58125, which did not modify **HO-1** mRNA stability. The induction of **HO-1** by NO and its potentiation by anti-inflammatory agents may play a role in inflammatory and immune responses.

L39 ANSWER 114 OF 131 MEDLINE on STN DUPLICATE 56
ACCESSION NUMBER: 2001435318 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11208485
TITLE: Significance of endothelial prostacyclin and nitric oxide in peripheral and pulmonary circulation.
AUTHOR: Gryglewski R J; Chlopicki S; Uracz W; Marcinkiewicz E
CORPORATE SOURCE: Jagiellonian University, 16 Grzegorzecka str., 31-531 Cracow, Poland.. mfgrygle@kinga.cyf-kr.edu.pl
SOURCE: Medical science monitor : international medical journal of experimental and clinical research, (2001 Jan-Feb) Vol. 7, No. 1, pp. 1-16.
Journal code: 9609063. ISSN: 1234-1010.
PUB. COUNTRY: Poland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 6 Aug 2001
Last Updated on STN: 6 Aug 2001
Entered Medline: 2 Aug 2001

AB BACKGROUND: Vasoprotective function of endothelial cells is associated, among others, with biosynthesis and release of nitric oxide (NO), prostacyclin (PGI2), **prostaglandin** E2 (PGE2), carbon monoxide (CO) and plasminogen activator (t-PA). These endothelial mediators calm down activated platelets and leukocytes, prevent the occurrence of parietal thrombotic events, promote thrombolysis, maintain tissue perfusion and protect vascular wall against acute damage and against chronic remodeling. Endothelial dysfunction in patients suffering from atherosclerosis or diabetes type 2 is associated not only with suppression in release of the above mediators but also with deleterious discharge of **prostaglandin** endoperoxides (PGH2, PGG2), superoxide anion (O2-, peroxynitrite (ONOO-), and plasminogen activator inhibitor (PAI-1). We looked for mechanisms of protective endothelial function, with a special respect to the differences between peripheral and pulmonary circulation. METHODS: Cultured endothelial cells of bovine aorta (BAEC) were used to study physiological and pharmacological mechanisms of increasing free cytoplasmic calcium [Ca2+]i. A porphyrinic sensor quantified the release of NO from BAEC. In cultured human umbilical vein endothelial cells (HUVEC) we looked for induction by bradykinin (Bk) of mRNAs for a number of enzymes. In blood perfused rat lungs we studied protective role of NO against injury inferred by lipopolysaccharide on pulmonary microcirculation that was accomplished by thromboxane A2 (TXA2), platelet activating factor (PAF),

cysteinyl-leukotrienes (cyst-LTs) and the complement system. In vivo we analyzed the influence of Bk, perindopril and quinapril ('tissue type' angiotensin converting enzyme inhibitors, ACE-Is) on endothelial function in entire circulation of anaesthetized rats using a thrombolytic bioassay and EIA for 6-keto-PGF1 alpha and t-PA antigen. RESULTS: In BAEC Bk via kinin B2 receptors raised in a concentration-dependent manner (1 pM-10 nM) free cytoplasmic calcium ions [Ca2+]i, that triggered the release of NO from BAEC. Calcium ionophore (A23187, 1-100 nM) as well as receptor agonists such as adenosine diphosphate (ADP, 10 nM-1 microM), adrenaline (Adr, 1-10 microM) or acetylcholine (Ach, 10-100 microM) produced a similar rise in endothelial [Ca2+]i as did Bk at a nanomolar concentration. 'Tissue type' ACE-Is, e.g. quinapril or perindopril acted through accumulation of endogenous Bk. However, the potency of ACE-I to change endothelial function is by several orders of magnitude lower than that for exogenous Bk. In vivo the major difference between thrombolytic actions by quinapril or perindopril on one hand, and by exogenous Bk on the other was longevity of thrombolysis by ACE I and a distinct hypotensive action of exogenous Bk. Still, the long-lasting isolated thrombolytic effect of ACE I was mediated entirely by endogenous BK as evidenced by the preventive action of icatibant, a kinin B2 receptor antagonist. Moreover, in vivo the immediate thrombolysis by ACE-I was mediated by PGI2 rather than by NO or t-PA, as shown by pharmacological analysis, and by direct blood assays of 6-keto-PGF1 alpha and t-PA antigen. Bradykinin as a mediator of pleiotropic endothelial action of several cardiovascular drugs (e.g. ACE-I) may complete its mission not only through B2 receptor and [Ca2+]i--mediated release of PGI2 or NO. Here, we describe a new route of the Bk action. Bk mediated induction of the [Ca2+]i-independent, so called 'inducible', endothelial isoenzymes required for generation of CO, PGI2 and PGE2. After 4 hours of incubation of HUVEC with Bk (10 nM) it induced mRNAs for haemooxygenase 1 (**HO-1**), cyclooxygenase 2 (COX-2), **prostaglandin** E synthase (PGE-S) whereas mRNA for nitric oxide synthase 2 (NOS-2) was weakly affected. We proved also that unlike in peripheral circulation, in pulmonary circulation only NO but not PGI2 would play a protective role. In the blood-perfused lung, endotoxaemia liberates lipids, such as TXA2, PAF and cyst-LTs. These toxic lipids along with the activated complement mediate pulmonary damage. Pulmonary endothelial nitric oxide is the only local protector against lung injury evoked by the phagocytised bacterial lipopolysaccharide. SUMMARY: Summing up, in peripheral circulation endogenous Bk is the most efficient activator of protective endothelial function. For instance, thrombolytic action of 'tissue type' ACE-I depends on the Bk-released PGI2. Acting as an agonist of endothelial B2 kinin receptors Bk rises [Ca2+]i with a subsequent activation of constitutive COX 1 and NOS-3. This is followed by an immediate release of PGI2 and NO. Moreover, acting as 'microcytokine' Bk induces mRNAs for **HO-1**, COX-2 and PGE S, the isoenzymes responsible for a delayed endothelial biosynthesis of CO, PGI2 and PGE2. (ABSTRACT TRUNCATED)

L39 ANSWER 115 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2000:457190 CAPLUS Full-text
DOCUMENT NUMBER:	133:85122
TITLE:	Expression vectors comprising multiple shear stress responsive elements (SSRE) and a gene of interest and modulating vasculogenesis and/or angiogenesis
INVENTOR(S):	Resnick, Nitzan
PATENT ASSIGNEE(S):	Florence Medical Ltd., Israel
SOURCE:	PCT Int. Appl., 61 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039275	A2	20000706	WO 1999-IL702	19991223
WO 2000039275	A3	20001026		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6440726	B1	20020827	US 1998-220510	19981224
AU 2000017954	A	20000731	AU 2000-17954	19991223
EP 1141266	A2	20011010	EP 1999-961261	19991223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002533113	T	20021008	JP 2000-591168	19991223
PRIORITY APPLN. INFO.:			US 1998-113863P P	19981224
			US 1998-220510 A	19981224
			US 1998-220510P P	19981224
			WO 1999-IL702 W	19991223

AB This invention provides expression vectors comprising multiple shear stress responsive elements (SSRE) and one or more genes of interest and methods of treating disorders related to or associated with vasculogenesis and/or angiogenesis conditions.

L39 ANSWER 116 OF 131 MEDLINE on STN DUPLICATE 57

ACCESSION NUMBER: 2001069807 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11078701
TITLE: 15-Deoxy-Delta(12,14)-**prostaglandin** J(2) facilitates thyroglobulin production by cultured human thyrocytes.
AUTHOR: Kasai K; Banba N; Hishinuma A; Matsumura M; Kakishita H; Matsumura M; Motohashi S; Sato N; Hattori Y
CORPORATE SOURCE: Department of Endocrinology and Metabolism, Dokkyo University School of Medicine, Mibu, Tochigi 321-0293, Japan.. kkasai@dokkyomed.ac.jp
SOURCE: American journal of physiology. Cell physiology, (2000 Dec) Vol. 279, No. 6, pp. C1859-69.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 4 Jan 2001

AB A cyclopentenone-type **prostaglandin**, 15-deoxy-Delta(12, 14)- **prostaglandin** J(2) (15-d-PGJ(2)), has been shown to induce the cellular stress response and to be a ligand for the peroxisome proliferator-activated receptor (PPAR)-gamma. We studied its effect on the basal and thyrotropin (TSH)-induced production of thyroglobulin (TG) by human thyrocytes cultured in the presence of 10% FBS. In 15-d-PGJ(2)-treated cells in which the agent itself did not stimulate cAMP production, both the basal production of TG and the response to

TSH were facilitated, including the production of TG and cAMP, whereas such production was decreased in untreated cells according to duration of culture. PGD(2) and PGJ(2), which are precursors to 15-d-PGJ(2), exhibited an effect similar to 15-d-PGJ(2). However, the antidiabetic thiazolidinediones known to be specific ligands for PPAR-gamma, and WY-14643, a specific PPAR-alpha ligand, lacked this effect. 15-d-PGJ(2) and its precursors, but not the thiazolidinediones, induced gene expression for heme oxygenase-1 (**HO-1**), a stress-related protein, and strongly inhibited interleukin-1 (IL-1)-induced nitric oxide (NO) production. Cyclopentenone-type PGs have been recently shown to inhibit nuclear factor-kappaB (NF-kappaB) activation via a direct and PPAR-independent inhibition of inhibitor-kappaB kinase, suggesting that, in human thyrocytes, such PGs may inhibit IL-1-induced NO production, possibly via an inhibition of NF-kappaB activation. On the other hand, sodium arsenite, a known activator of the stress response pathway, induced **HO-1** mRNA expression but lacked a promoting effect on TG production. Thus 15-d-PGJ(2) and its precursors appear to facilitate TG production via a PPAR-independent mechanism and through a different pathway from the cellular stress response that is available to cyclopentenone-type PGs. Our findings reveal a novel role of these PGs associated with thyrocyte differentiation.

L39 ANSWER 117 OF 131 MEDLINE on STN DUPLICATE 58

ACCESSION NUMBER: 2001127812 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11137620
TITLE: Resolution of inflammation.
AUTHOR: Willoughby D A; Moore A R; Colville-Nash P R; Gilroy D
CORPORATE SOURCE: Department of Experimental Pathology, William Harvey Research Institute, St Bartholomew's and Royal London School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK.
SOURCE: International journal of immunopharmacology, (2000 Dec) Vol. 22, No. 12, pp. 1131-5. Ref: 18
Journal code: 7904799. ISSN: 0192-0561.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 22 Feb 2001

AB Acute inflammatory reactions, in contrast to chronic inflammatory reactions, are usually self-limiting and resolve. We have investigated the resolving phase of a number of immune and non-immune inflammatory reactions induced in the pleural cavity of rats. COX-2 is expressed during resolution of these models. Using carrageenan pleurisy, we showed that this enzyme has a proinflammatory role as the reaction develops but an antiinflammatory role as the lesion resolves. This antiinflammatory role is associated with production of cyclopentenone **prostaglandins** and the absence of PGE2. Dual COX-1/COX-2 inhibitors or COX-2 inhibitors when given at the peak of the inflammatory response delay resolution, an effect reversed by replacing CyPGs into the pleural space. PGF2alpha like the CyPGs appears to have a role in resolving this reaction. Stress proteins are also induced in a variety of acute inflammatory models during resolution. Heme oxygenase-1 (**HO -1**) is one such protein so too are members of the hsp70 family. An inducer of **HO-1** promotes resolution whereas an inhibitor is proinflammatory. In most cases it appears to be the macrophage that is the source of proteins necessary for resolution to occur. Understanding how proinflammatory pathways switch to the antiinflammatory pathways necessary for resolution to take place may

eventually allow the exploitation of endogenous antiinflammatory pathways in the treatment of chronic inflammation.

L39 ANSWER 118 OF 131 MEDLINE on STN
ACCESSION NUMBER: 2001078004 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10975414
TITLE: Oxidative stress in prostatic fluid of patients with chronic pelvic pain syndrome: correlation with gram positive bacterial growth and treatment response.
AUTHOR: Shahed A R; Shoskes D A
CORPORATE SOURCE: Division of Urology, Harbor-UCLA Medical Center, Torrance, California, USA.
CONTRACT NUMBER: R01 DK53738 (NIDDK)
SOURCE: Journal of andrology, (2000 Sep-Oct) Vol. 21, No. 5, pp. 669-75.
Journal code: 8106453. ISSN: 0196-3635.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 11 Jan 2001

AB The etiology of chronic pelvic pain syndrome (CPPS)/chronic prostatitis category III remains unknown. Whereas a subset of men respond to antimicrobial therapy, gram positive bacteria isolated from expressed prostatic secretions (EPS) are often considered to be commensal rather than pathogenic. We wished to study oxidative stress as a marker of tissue injury and response in EPS of men with CPPS to determine whether infection with gram positive bacteria is associated with increased oxidative stress. A total of 300 EPS specimens from 100 men with CPPS were collected for microscopy, culture, and biochemical and molecular assays. Oxidant injury was measured by 8-isoprostane F2alpha (IsoP) levels and total antioxidant capacity as Trolox equivalents. Total RNA from EPS was used for gene expression of heme oxygenase-1 (**HO- 1**) and granzyme B. The only bacteria found in EPS were gram positive. For our analysis, these men were classified as having chronic bacterial prostatitis (category II). IsoP levels (pg/mL) were highest in men with category II prostatitis (7315 +/- 1428) followed by nonbacterial prostatitis (category IIIa, 2043 +/- 561), prostatodynia (category IIIb, 319 +/- 81), and asymptomatic controls (298 +/- 99). IsoP levels decreased significantly after successful treatment with antibiotics or an antioxidant supplement (Prosta-Q). Antioxidant capacity was detected in 11 out of 18, 4 out of 16, and 1 out of 16 men tested with category II, IIIa, and IIIb prostatitis, respectively. No correlation was observed between IsoP levels and the number of white blood cells in EPS. **HO-1** and granzyme B expression was highest in men with category II prostatitis than in men with either category III prostatitis or asymptomatic controls. On the basis of elevated oxidative stress, clinical response to antibiotics, and post-treatment reduction in oxidative stress, we conclude that gram positive bacteria in some men with CPPS may be pathogens. It is speculated that oxidative stress may be a key pathway in some men with CPPS that can be targeted with antioxidant therapy.

L39 ANSWER 119 OF 131 MEDLINE on STN DUPLICATE 59
ACCESSION NUMBER: 2001086400 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11118808
TITLE: Unilateral upregulation of cyclooxygenase-2 following

cerebral, cortical photothrombosis in the rat: suppression by MK-801 and co-distribution with enzymes involved in the oxidative stress cascade.

AUTHOR: Bidmon H J; Oermann E; Schiene K; Schmitt M; Kato K; Asayama K; Witte O W; Zilles K

CORPORATE SOURCE: C.&O. Vogt Institute of Brain Research, Building 22.03.05, Heinrich-Heine-University, Moorenstrasse. 5, D-40225 Dusseldorf, Germany.. hjb@hirn.uni-duesseldorf.de

SOURCE: Journal of chemical neuroanatomy, (2000 Nov) Vol. 20, No. 2, pp. 163-76.
Journal code: 8902615. ISSN: 0891-0618.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200101

ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 18 Jan 2001

AB Cyclooxygenase-2 (COX-2) is an essential enzyme for **prostaglandin** synthesis from arachidonic acid, during which considerable amounts of superoxide are produced. During pathological conditions, superoxide and nitric oxide (NO) rapidly form peroxynitrite, a potent cytotoxin, causing symptoms referred to as oxidative stress response. Superoxide is controlled by enzymes such as manganese- or copper-zinc-dependent superoxide dismutase (Mn-SOD, CuZn-SOD), glutathione peroxidase (GPx) and antioxidants derived from heme oxygenase (HO) activity such as biliverdin and bilirubin. NO derives from 3 NO-synthases (NOS I-III) from which the calcium-dependent NOS-I and III are activated rapidly due to hyperexcitation. We studied the induction of COX-2 by immunohistochemistry at days 1, 2 and 5 following cortical photothrombosis in normal and MK-801 treated rats. The results showed a weak constitutive, neuronal expression of COX-2 in cortex and amygdala. Layers II+III contained considerably more COX-2 than infragranular layers. One and 2 days following injury COX-2 was highly upregulated in the supragranular layers of the whole injured hemisphere compared with sham-operated animals and compared to the contralateral unlesioned hemisphere, whereas at day 5 COX-2 levels had returned to baseline. MK-801 treatment caused a reduction in COX-2 upregulation at day one and by day 2 no significant differences between injured and contralateral hemisphere were measurable. COX-2 positive neurons were found in close association with NOS-I containing neurons and their fibers but were not colocalized. In addition, codistribution of COX-2 was found with **HO-1**, CuZn-SOD and GPx containing cells, whereas COX-2 was colocalized with HO-2 and/or MnSOD in cortical neurons.

L39 ANSWER 120 OF 131 MEDLINE on STN DUPLICATE 60

ACCESSION NUMBER: 2000384879 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 10837804

TITLE: Cyclopentenone **prostaglandin** 15-deoxy-Delta(12,14)-**prostaglandin** J(2) acts as a general inhibitor of inflammatory responses in activated BV-2 microglial cells.

AUTHOR: Koppal T; Petrova T V; Van Eldik L J

CORPORATE SOURCE: Department of Cell and Molecular Biology, Northwestern University Medical School, Ward 4-202, 303 E. Chicago Avenue, Chicago, IL 60611, USA.

CONTRACT NUMBER: AG00260 (NIA)
AG13939 (NIA)
AG15501 (NIA)

SOURCE: Brain research, (2000 Jun 9) Vol. 867, No. 1-2, pp. 115-21.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 18 Aug 2000
Last Updated on STN: 18 Aug 2000
Entered Medline: 4 Aug 2000

AB 15-deoxy-Delta(12,14)-PGJ(2), a cyclopentenone derivative of PGD(2), was recently reported [Petrova et al., Proc. Natl. Acad. Sci. USA 96 (1999) 4668-4673] to suppress inducible nitric oxide synthase (iNOS) production in microglia and mixed glial cultures stimulated with lipopolysaccharide (LPS). We report here that in addition to suppressing iNOS production, 15d-PGJ(2) also decreases the production of tumor necrosis factor alpha (TNFalpha), interleukin-1 beta (IL-1beta) and cyclooxygenase-2 (COX-2) in LPS-stimulated BV-2 microglial cells, thereby acting as a general inhibitor of microglial activation. Concomitantly, 15d-PGJ(2) itself up-regulates the production of the antioxidant enzyme heme oxygenase-1 (**HO-1**) and increases intracellular total glutathione levels. To test if increased **HO-1** levels were involved in the ability of 15d-PGJ(2) to block microglial activation, we used a **HO-1** inhibitor that could block the activity of **HO-1**. The presence of the **HO -1** inhibitor did not alter the 15d-PGJ(2)-induced inhibition of LPS-stimulated iNOS and TNFalpha protein levels, and led to only a partial reduction in the protection offered by 15d-PGJ(2) against LPS-induced nitrite production. These results suggest that **HO-1** upregulation by 15d-PGJ(2) is not the primary pathway responsible for the anti-inflammatory action of 15d-PGJ(2) in microglial cells.

L39 ANSWER 121 OF 131 MEDLINE on STN DUPLICATE 61
ACCESSION NUMBER: 2000243373 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10780998
TITLE: Enhanced expression of haem oxygenase-1 by nitric oxide and antiinflammatory drugs in NIH 3T3 fibroblasts.
AUTHOR: Alcaraz M J; Habib A; Lebret M; Creminon C; Levy-Toledano S; Maclouf J
CORPORATE SOURCE: Unite 348 INSERM, Institut Federatif de Recherche Lariboisiere-Circulation, 75475 Paris cedex 10, France.
SOURCE: British journal of pharmacology, (2000 May) Vol. 130, No. 1, pp. 57-64.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 6 Jul 2000
Last Updated on STN: 20 Jul 2000
Entered Medline: 27 Jun 2000

AB 1. Haem oxygenase-1 (**HO-1**) can exert protective effects against oxidative stress and inflammation. Fibroblasts participate in inflammatory responses where they produce high levels of **prostaglandins** (PGs) and nitric oxide (NO). However, little is known of the presence of **HO-1** in these cells and the possible interactions among these pathways. Incubation of cells with NO donors, spermine nonoate (SPNO) and S-nitroso-N-acetylpenicillamine (SNAP), induced a dose- and time-dependent expression of **HO- 1** protein. 2. NO donors

increased basal PGE(2) release although they reduced PGE(2) accumulated in the medium and cyclo-oxygenase (COX) activity when cells were stimulated with lipopolysaccharide (LPS). COX-2 protein was weakly induced by SPNO in basal conditions and in the presence of LPS a synergy for **HO-1** and COX-2 protein expression was observed. 3. Our results indicate that reactive oxygen species participate in the inductive effect of NO donors or LPS on **HO- 1** expression, whereas endogenous NO production may play a role in the mechanism of the synergy exhibited by SPNO and LPS on **HO- 1** and COX-2 expression. In this system, zinc protoporphyrin IX did not affect nitrite levels but reduced COX activity. 4. The selective COX-2 inhibitors SC58125 and NS398 as well as the non-selective COX inhibitor, indomethacin, strongly reduced PGE(2) synthesis and showed a synergy with NO donors in **HO-1** and COX-2 induction. Addition of PGE(2) had no effect, suggesting a mechanism independent of PGs formation. 5. In inflammatory conditions a number of factors could cooperate to induce **HO-1** and COX-2, with a positive regulation by COX inhibitors.

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ACCESSION NUMBER: 2001:109283 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100109283
TITLE: COX-2 induction after cortical focal ischemia: suppression by MK-801 and codistribution with enzymes involved in the oxidative stress cascade.
AUTHOR(S): Bidmon, H. J. [Reprint author]; Oermann, E.; Schiene, K.; Witte, O. W.; Zilles, K.
CORPORATE SOURCE: Duesseldorf University, Duesseldorf, Germany
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-670.4. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Feb 2001
Last Updated on STN: 15 Feb 2002

AB COX-2 is an essential enzyme for **prostaglandin** synthesis from arachidonic acid liberating considerable amounts of superoxide (SO). During pathological conditions SO and nitric oxide (NO) rapidly form peroxynitrite, a potent cytotoxin causing oxidative stress. SO is controlled by manganese- or copper-zinc- dependent superoxide dismutase (Mn-SOD, CuZn-SOD), glutathione peroxidase (GPx) and antioxidants derived from heme oxygenase (HO) activity such as biliverdin and bilirubin. NO derives from 3 NO-synthases (NOS I-III) which are rapidly activated after ischemia. We studied the induction of COX-2 by immunohistochemistry at days 1, 2, and 5 following cortical photothrombosis in untreated and MK-801 treated as well as in sham-lesioned control rats. The results showed a weak constitutive, neuronal expression of COX-2 in cortex and amygdala of control rats. Layers II+III contained always considerably more COX-2 than infragranular layers. One and 2 days following injury COX-2 was highly upregulated in the supragranular layers of the whole injured hemisphere compared to sham-operated animals and compared to the contralateral unlesioned hemisphere, whereas at day 5 COX-2 levels had returned to baseline. MK-801 treatment caused a reduction in COX-2 expression. COX-2 positive neurons were closely associated and intermingled with cells expressing NOS, **HO-1**, CuZn-SOD and cGPx, whereas COX-2, HO-2 and MnSOD were co-localized, suggesting an intracellular, protective, antioxidative efficacy of bilirubin and MnSOD.

L39 ANSWER 123 OF 131 MEDLINE on STN
ACCESSION NUMBER: 2000031247 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10566971
TITLE: Phosphorylation of c-Jun and its localization with heme oxygenase-1 and cyclooxygenase-2 in CA1 pyramidal neurons after transient forebrain ischemia.
AUTHOR: Matsuoka Y; Okazaki M; Zhao H; Asai S; Ishikawa K; Kitamura Y
CORPORATE SOURCE: Department of Neurobiology, Kyoto Pharmaceutical University, Yamashina, Japan.
SOURCE: Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism, (1999 Nov) Vol. 19, No. 11, pp. 1247-55. Journal code: 8112566. ISSN: 0271-678X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 13 Jan 2000
Last Updated on STN: 13 Jan 2000
Entered Medline: 30 Nov 1999

AB Accumulating evidence on the molecular and cellular basis of ischemia/reperfusion-induced neurodegeneration suggests that oxidative stress is involved. Heme oxygenase (HO) and cyclooxygenase (COX) play physiologically important roles in the CNS. Conversely, HO and COX also can increase oxidative stress. Recent studies suggest that c-Jun phosphorylation is an important step in some forms of stress-induced neuronal apoptosis. In this study, the authors tried to clarify the association of HO and COX with c-Jun phosphorylation. Inducible forms of HO and COX (**HO-1** and COX-2, respectively) were transiently induced in CA1 pyramidal neurons after ischemia. c-Jun also was induced in pyramidal neurons throughout the hippocampal formation, but its phosphorylation was limited to CA1. In contrast, these molecules were constitutively expressed at low levels. Most (84%) of the CA1 pyramidal neurons examined expressed **HO-1**, COX-2, or both, and such expression showed good co-localization with c-Jun phosphorylation. These results suggest the following: (1) c-Jun phosphorylation was associated with ischemia/reperfusion-induced neuronal apoptosis; (2) **HO-1** and COX-2 were induced in CA1 pyramidal neurons, which undergo cell death; and (3) most CA1 pyramidal neurons expressed **HO-1**, COX-2, or both, which strongly suggests that these are candidates for neuron killers.

L39 ANSWER 124 OF 131 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:286077 BIOSIS Full-text
DOCUMENT NUMBER: PREV199900286077
TITLE: The regulatory role of heme oxygenase on the cyclooxygenase pathway.
AUTHOR(S): Haider, A. [Reprint author]; Ferreri, N. R. [Reprint author]; Abraham, N. G. [Reprint author]
CORPORATE SOURCE: New York Medical College, Valhalla, NY, USA
SOURCE: FASEB Journal, (March 15, 1999) Vol. 13, No. 5 PART 2, pp. A781. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 99. Washington, D.C., USA. April 17-21, 1999. Federation of American Societies for Experimental Biology.
CODEN: FAJOEC. ISSN: 0892-6638.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Jul 1999
Last Updated on STN: 28 Jul 1999

L39 ANSWER 125 OF 131 MEDLINE on STN DUPLICATE 62
ACCESSION NUMBER: 1999217911 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10203248
TITLE: Activators of peroxisome proliferator-activated receptor-gamma (PPARgamma) inhibit inducible nitric oxide synthase expression but increase heme oxygenase-1 expression in rat glial cells.
AUTHOR: Kitamura Y; Kakimura J; Matsuoka Y; Nomura Y; Gebicke-Haerter P J; Taniguchi T
CORPORATE SOURCE: Department of Neurobiology, Kyoto Pharmaceutical University, Japan.
SOURCE: Neuroscience letters, (1999 Mar 5) Vol. 262, No. 2, pp. 129-32.
Journal code: 7600130. ISSN: 0304-3940.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 15 Jul 1999
Last Updated on STN: 4 Feb 2003
Entered Medline: 2 Jul 1999

AB The peroxisome proliferator-activated receptor-gamma (PPARgamma) is activated by 15-deoxy-delta(12,14) **prostaglandin** J2 (15d-PGJ2), anti-diabetic thiazolidinediones and several non-steroidal anti-inflammatory drugs (NSAIDs). In rat glial cells, lipopolysaccharide and interferon-gamma (LPS/IFN-gamma) induced expression of both inducible nitric oxide synthase (iNOS) and heme oxygenase-1 (**HO-1**). PPARgamma activators inhibited iNOS expression by LPS and IFN-gamma. However, PPARgamma activator alone induced **HO-1** expression and further enhanced LPS/IFN-gamma-induced **HO- 1** expression. These results suggest that activation of PPARgamma negatively regulate iNOS expression and positively regulates **HO- 1** expression in glial cells.

L39 ANSWER 126 OF 131 MEDLINE on STN
ACCESSION NUMBER: 1999097105 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9880398
TITLE: Spreading depression-induced gene expression is regulated by plasma glucose.
AUTHOR: Koistinaho J; Pasonen S; Yrjanheikki J; Chan P H
CORPORATE SOURCE: A.I. Virtanen Institute, University of Kuopio, Finland.. jari.koistinaho@uku.fi
SOURCE: Stroke; a journal of cerebral circulation, (1999 Jan) Vol. 30, No. 1, pp. 114-9.
Journal code: 0235266. ISSN: 0039-2499.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 23 Feb 1999
Last Updated on STN: 3 Mar 2000

Entered Medline: 8 Feb 1999

AB BACKGROUND AND PURPOSE--Plasma glucose and spreading depression (SD) are both determinants of brain ischemia. The purpose of this study was to examine whether plasma glucose affects SD-induced gene expression in the cortex. METHODS--SD was induced by topical application of KCl. Hyperglycemia and hypoglycemia were induced by intraperitoneal injection of glucose and insulin, respectively. The expression of c-fos, cyclooxygenase-2 (COX-2), protein kinase C-delta (PKCdelta), and heme oxygenase-1 (**HO-1**) was determined by in situ hybridization. RESULTS--SD alone induced expression of c-fos (by 340%), COX-2 (210%), **HO-1** (470%), and PKCdelta (410%). Hypoglycemia (2.4+/-0.9 mmol/L) alone did not induce gene expression, and hyperglycemia (22.1+/-3.7 mmol/L) alone induced only c-fos by 42%. When hypoglycemia was induced 30 minutes before SD, c-fos induction was enhanced by 145%, but the induction of **HO-1** and PKCdelta was reduced to 43% and 64%, respectively. When hyperglycemia was induced 30 minutes before SD, c-fos induction was enhanced by 388% and COX-2 expression by 53%, whereas the induction of PKCdelta and **HO -1** was reduced to 54% and 51%, respectively. The frequency, amplitude, and duration of direct current potentials were unaltered in hyperglycemic SD animals, whereas in hypoglycemic animals the duration was increased by 47%. CONCLUSIONS--While SD induces expression of several genes, the availability of glucose regulates the extent of the gene induction. The effect of glucose is different on early-response genes (c-fos and COX-2) compared with late-response genes. Plasma glucose may contribute to neuronal damage partially by regulating gene expression.

L39 ANSWER 127 OF 131 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:43679 CAPLUS Full-text
DOCUMENT NUMBER: 128:97167
TITLE: Oxidative stress produced by drugs and chemicals and the induction of heme oxygenase
AUTHOR(S): Yoshida, Takemi
CORPORATE SOURCE: Department of Biochemical Toxicology, School of Pharmaceutical Sciences, Showa University, Tokyo, Japan
SOURCE: Yakubutsu Dotai (1997), 12(5), 531-542
CODEN: YADOEL; ISSN: 0916-1139
PUBLISHER: Nippon Yakubutsu Dotai Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 81 refs. Evidence has been accumulating that oxidative stress plays important roles in pathogenesis of various acute and chronic diseases. A wide variety of drugs and chems. have been shown to produce reactive oxygen species by their oxidative metabolism in the body, thus may cause oxidative stress and lead to cellular and tissue damages. In order to response to such oxidative insults, many antioxidative defense systems are constitutively expressed in mammalian cells the body. Of these antioxidative defense systems, heme oxygenase-1 (**HO-1**), a first and rate-limiting enzyme of heme degradation, has recently been shown to be highly responsible enzyme against oxidative stress. HO oxidatively cleaves heme into carbon monoxide (CO), Fe2+ and biliverdin, the latter is readily reduced to bilirubin. These degradative byproducts of heme by HO has currently been characterizing their physiol. importance. Namely, CO, as just like NO, may play as gaseous messenger; bilirubin acts as an antioxidant; Fe2+ is a modulator of ferritin. Therefore, the induction of **HO-1** produced by physiol. and pathophysiol. states, and by drugs and chems. may play vital roles in the adaptive and/or protective response to oxidative stress as a whole. Accumulated evidence demonstrates that **HO-1** is induced by not only the substrate heme but also a wide variety of divergent drugs and chems., such as hormones, heavy metals, organic compds. including glutathione depletors, cytokines, **prostaglandins** and so on. Although

a detailed mechanism of the induction of **HO-1** by these compds. remains to be determined, most of them produce the enzyme induction through oxidative stress. Addnl., it is well established that **HO-1** induction in lier or kidney is generally followed by the decrease in cytochrome P 450 content, important enzyme(s) which metabolizes endogenous substances and exogenous drugs and chems. This review will describe partly on the current understanding of physiol. and/or pathophysiol. significance of **HO-1**, and mainly focus on the significance of this enzyme induction in response to oxidative stress produced by drugs and chems. I hope that this review will stimulate interest and understandings in **HO-1** and its potential roles in response to oxidative stress.

L39 ANSWER 128 OF 131 MEDLINE on STN
ACCESSION NUMBER: 97053701 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8898115
TITLE: Quinazoline derivatives suppress nitric oxide production by macrophages through inhibition of NOS II gene expression.
AUTHOR: Fujiwara N; Okado A; Seo H G; Fujii J; Kondo K; Taniguchi N
CORPORATE SOURCE: Department of Biochemistry, Osaka University Medical School, Japan.
SOURCE: FEBS letters, (1996 Oct 21) Vol. 395, No. 2-3, pp. 299-303. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 20 Dec 1996

AB We have found three novel quinazolidine derivatives which inhibit the formation of nitrite dose-dependently in a murine macrophage cell line, RAW264.7. The decreased nitrite formation was due not to the inhibition of nitric oxide synthase activity but to suppression of NOS II mRNA and protein expression. In rat vascular smooth muscle cells (VSMC), however, these compounds rather enhanced NOS II mRNA. These compounds also prevented LPS-stimulated heme oxygenase-1 (**HO-1**) and cyclooxygenase-2 (COX-2) gene expression in RAW264.7 cells, but again not in VSMC. The three quinazolidine derivatives specifically inhibit gene expression of NOS II, **HO-1** and COX-2 only in macrophage cells, indicating that they are selective inhibitors of inducible gene expression in macrophages.

L39 ANSWER 129 OF 131 MEDLINE on STN DUPLICATE 63
ACCESSION NUMBER: 96285313 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8679227
TITLE: Heme oxygenase-1: function, regulation, and implication of a novel stress-inducible protein in oxidant-induced lung injury.
AUTHOR: Choi A M; Alam J
CORPORATE SOURCE: Division of Pulmonary and Critical Care, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
SOURCE: American journal of respiratory cell and molecular biology, (1996 Jul) Vol. 15, No. 1, pp. 9-19. Ref: 58
Journal code: 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 28 Aug 1996
Last Updated on STN: 6 Feb 1998
Entered Medline: 20 Aug 1996

AB Accumulating evidence suggests that oxidative stress plays a central role in the pathogenesis of many pulmonary diseases including adult respiratory distress syndrome, emphysema, asthma, bronchopulmonary dysplasia, and interstitial pulmonary fibrosis. The morbidity and mortality of these diseases remain high even with optimal medical management. In our attempts to devise new therapies for these disorders, it is crucial to improve our understanding of the basic mechanism(s) of oxidant-induced lung injury. A major line of investigation seeks to characterize the cellular and molecular responses of the lung to oxidant insults. Much progress has been made in our understanding of the role of the "classic" antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase) in mediating the lung's resistance against oxidant lung injury. However, it is becoming clear that other oxidant-induced gene products may also play vital roles in the lung's adaptive and/or protective response to oxidative stress. One such stress-response protein is heme oxygenase-1, **HO-1**. Since the identification of **HO-1** in 1968, many of the studies involving this enzyme were understandably focused on the regulation and function of **HO-1** in heme metabolism. This emphasis is self-evident as **HO-1** catalyzes the first and rate-limiting step in heme degradation. Interestingly, however, evidence accumulated over the past 25 years demonstrates that **HO-1** is induced not only by the substrate heme but also by a variety of non-heme inducers such as heavy metals, endotoxin, heat shock, inflammatory cytokines, and **prostaglandins**. The chemical diversity of **HO-1** inducers led to the speculation that **HO-1**, besides its role in heme degradation, may also play a vital function in maintaining cellular homeostasis. Further support for this hypothesis was provided by Tyrrell and colleagues who showed in 1989 that **HO-1** is also highly induced by a variety of agents causing oxidative stress. Subsequently, many investigators have focused their attention on the function and regulation of **HO-1** in various in vitro and in vivo models of oxidant-mediated cellular and tissue injury. The magnitude of **HO-1** induction after oxidative stress and the wide distribution of this enzyme in systemic tissues coupled with the intriguing biological activities of the catalytic byproducts, carbon monoxide, iron, and bilirubin, makes **HO-1** a highly attractive and interesting candidate stress-response protein which may play key role(s) in mediating protection against oxidant-mediated lung injury. This review will focus on the current understanding of the physiological significance of **HO-1** induction and the molecular regulation of **HO-1** gene expression in response to oxidative stress. We hope that this discussion will stimulate interest and investigations into a field which is still largely uncharted in the pulmonary research community.

L39 ANSWER 130 OF 131 MEDLINE on STN DUPLICATE 64
ACCESSION NUMBER: 95394942 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7665598
TITLE: Identification of a cis-regulatory element for delta 12-**prostaglandin** J2-induced expression of the rat heme oxygenase gene.
AUTHOR: Koizumi T; Odani N; Okuyama T; Ichikawa A; Negishi M
CORPORATE SOURCE: Department of Physiological Chemistry, Faculty of Pharmaceutical Sciences, Kyoto University, Japan.
SOURCE: The Journal of biological chemistry, (1995 Sep 15) Vol. 270, No. 37, pp. 21779-84.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 20 Oct 1995
Last Updated on STN: 6 Feb 1998
Entered Medline: 12 Oct 1995

AB We recently reported that delta 12-**prostaglandin** (PG) J2 caused various cells to synthesize heme oxygenase, **HO-1** (Koizumi, T., Negishi, M., and Ichikawa, A. (1992) **Prostaglandins** 43, 121-131). Here we examined the molecular mechanism underlying the delta 12-PGJ2-induced **HO-1** synthesis. delta 12-PGJ2 markedly stimulated the promoter activity of the 5'-flanking region of the rat **HO-1** gene from -810 to +101 in rat basophilic leukemia cells. From functional analysis of various deletion mutant genes we found that the delta 12-PGJ2-responsive element was localized in a region from -690 to -660, containing an E-box motif, which was essential for the delta 12-PGJ2-stimulated promoter activity. When the region containing the delta 12-PGJ2-responsive element was combined with a heterologous promoter, SV40 promoter, in the sense and antisense direction, the element showed an enhancer activity in response to delta 12-PGJ2. Gel mobility shift assays demonstrated that delta 12-PGJ2 specifically stimulated the binding of two nuclear proteins to the E-box motif of this region. These results indicate that delta 12-PGJ2 induces the expression of the rat **HO-1** gene through nuclear protein binding to a specific element having an E-box motif.

L39 ANSWER 131 OF 131 'MEDLINE on STN DUPLICATE 65
ACCESSION NUMBER: 96000222 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7556684
TITLE: Involvement of protein kinase in delta 12-**prostaglandin** J2-induced expression of rat heme oxygenase-1 gene.
AUTHOR: Negishi M; Odani N; Koizumi T; Takahashi S; Ichikawa A
CORPORATE SOURCE: Department of Physiological Chemistry, Faculty of Pharmaceutical Sciences, Kyoto University, Japan.
SOURCE: FEBS letters, (1995 Sep 25) Vol. 372, No. 2-3, pp. 279-82.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
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AB We recently identified the cis-regulatory element and its specific nuclear binding factors for delta 12-**prostaglandin** (PG) J2-induced expression of the rat heme oxygenase, **HO-1** [Koizumi, T., Odani, N., Okuyama, T., Ichikawa, A. and Negishi, M. (1995) J. Biol. Chemical 270, in press]. Here we further examined the molecular mechanism underlying the delta 12-PGJ2-induced **HO-1** gene expression. Protein kinase inhibitors, 2-aminopurine and staurosporine, suppressed the delta 12-PGJ2-induced HO-1 mRNA and the nuclear protein binding to the delta 12-PGJ2-responsive cis-regulatory element in rat basophilic leukemia cells. Furthermore, the nuclear protein binding to the element was suppressed by in vitro phosphatase treatment of the nuclear proteins from delta 12-PGJ2-treated cells. These findings suggest that delta 12-PGJ2